PSJ15 Exh 24

PHARMA/DOSAGE - DOMESTIC DRUG DATA ENTRY/INDEX FORM

DRUG PRODUCT

Product/Chemical Name Meperidine Hydrochloride Tablets USP

Does this Document pertain to **all** Strengths? X Yes ___No

If **No**, enter strengths covered by this submission:

OTHER

Date: 07-28-05

CODE (GRTS Location):

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☐ Reference Authorization ☐ Export Authorization

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☐ Labeling Letter ☐ Phase 4 Commitment

Notes (Internal notes and correspondence)
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☐ ADR Quarterly/PSUR	☐ Pre-submission	☐ ADR Follow UP	☐ Resubmission
☐ ANDA (Abbreviated New Drug App.)		☐ Amendment	☐ Summary Basis of Approval
☐ Annual Report	☐ Supplement CBE –0 (FDA)	☒ Advertising	☐ Supplement CBE-30 (FDA)
☐ DMF	☐ Prior Approval Supplement (FDA)		☐ Supplement

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ID NUMBER:
(DMF#, ANDA#, NDA,)

ANDA 40-352

Sent from: Russell D. Reed

Sent To: DDMAC

Prepared by: Jenny Rowlett

Description: Postcard – Drug Store News "Opioids in Pain Management" – Leave Behinds for Wholesalers, Chains, Pharmacists

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TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE

1. DATE SUMBITTED
July 28, 2005

2. LABEL REVIEW NO. *(Biologics)*

Form Approved: OMB No. 0910-0001
Expiration Date: March 31, 2005
See OMB Statement on Reverse Part 1

3. NDA/ANDA/AADA OR BLA/PLA/PMA

Number: 76-412

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Morphine Sulfate Extended-Release Tablets	Morphine Sulfate Extended-Release Tablets Prod. Code No. 8315, 8330, 8380	050204	Mallinckrodt Inc. License No. *(Biologics)*

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9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT
Russell D. Reed
Labeling Manager

10. SIGNATURE OF RESPONSIBLE OFFICIAL
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11. APPLICANT'S RETURN ADDRESS
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St. Louis, MO 63134

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76-412	Morphine Sulfate Extended-Release Tablets	Morphine Sulfate Extended-Release Tablets	8315 (15 mg) 8330 (30 mg) 8380 (60 mg)	050204
76-438	Morphine Sulfate Extended-Release Tablets	Morphine Sulfate Extended-Release Tablets	8390 (100 mg) 8320 (200 mg)	050204
76-758	Oxycodone Hydrochloride Tablets USP	Oxycodone Hydrochloride Tablets USP	8515 (15 mg) 8530 (30 mg)	122603
76-855	Hydromorphone Hydrochloride Tablets USP	Hydromorphone Hydrochloride Tablets USP	3249 (8 mg)	050104
40-352	Meperidine Hydrochloride Tablets USP	Meperidine Hydrochloride Tablets USP	7113 (50 mg) 7115 (100 mg)	111202
40-050	Methadose® Oral Tablets	Methadone Hydrochloride Tablets USP	6974 (5 mg) 3454 (10 mg)	122902
17-116	Methadose® Oral Concentrate *and* Methadose® Sugar-Free Oral Concentrate	Methadone Hydrochloride Oral Concentrate USP	0527 (10 mg/mL) *and* 8725 (10 mg/mL)	072302 *and* 072502
74-184	Methadose® Dispersible Tablets	Methadone Hydrochloride Tablets USP	0540 (40 mg)	112104
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DRUG STORE NEWS
CONTINUING EDUCATION QUARTERLY

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This program is worth two contact hours (0.2 CEUs)

Target Audience
Pharmacists in community-based practice

Program Goal
To improve the pharmacist's ability to provide pain management

Learning Objectives
Upon completion of this program, the pharmacist should be able to:
1. Know the definition of pain and the characteristics of different types of pain
2. Advocate the use of pain assessment
3. Describe the differences of opioids used in the management of pain
4. Perform dosing conversions using the concepts associated with equianalgesic dosing of opiates

See the Spring 2005 issue of *Drug Store News CE Quarterly* for information on this program.

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By Joseph R. Ineck, Pharm.D., clinical specialist in pain management and palliative care, assistant professor Department of Pharmacy Practice, Creighton University School of Pharmacy and Health Professions and Carla Rubingh, Pharm.D., assistant professor Department of Pharmacy Practice University of Nebraska Medical Center College of Pharmacy

Universal Program Number: 401-000-05-009-H01
Initial release date: May 1, 2005
Planned expiration date: May 1, 2008
This program is worth two contact hours (0.2 CEUs).

Target Audience
Pharmacists in community-based practice

Program Goal
To improve the pharmacist's ability to provide pain management

Learning Objectives
Upon completion of this program, the pharmacist should be able to:

1. know the definition of pain and the characteristics of different types of pain.
2. advocate the use of pain assessment.
3. describe the differences of opioids used in the management of pain.
4. perform dosing conversions using the concepts associated with equianalgesic dosing of opiates.
5. explain the role of methadone in pain management and describe methadone dosing.

To obtain credit: Answer the questions at the end of this lesson on the answer sheet provided. If you are submitting your answers by mail or fax, completely fill in the circle corresponding to your answer with a black pen (no pencils or blue pens please). A statement of credit will be sent to participants achieving a minimum score of 70 percent correct responses. Statements of credit are issued within seven days of receipt if submitted by mail or fax and immediately if submitted online. Questions regarding statements of credit and other customer service issues should be directed to Angela Sims at (800) 933-9666.

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Pharmacist pain management: a focus on opioids and conversion issues

INTRODUCTION

We are currently living in the period dubbed the "decade of pain." This decade was described in such terms with great plans of advancing research and drug development and in improving clinical practice, which would lead to overall improvement in patient outcomes. Pain is the most frequent reason why patients seek out health care.[1] At any given time, it is estimated that 50 percent of the U.S. population suffers from some sort of pain and that 20 percent to 30 percent of the population suffers from serious pain.[1] It is estimated that pain costs the American public more than $100 billion each year in health care, compensation and litigation.[2] Lost productivity due to common pain conditions was estimated to cost $61.2 billion each year.[3] Those numbers are staggering and show the need for a decade devoted to the advancement of pain medicine and management.

We long have struggled with the many barriers to pain management, be they provider barriers, pharmacist barriers or patient barriers (Table 1).[4] Negative attitudes between providers and patients regarding the use of opioids have limited the use of medications significantly. Perceived regulatory barriers have intimidated some providers into restrictive prescribing practices. Negative media reports have scared many patients and their families into poor pain management by avoiding the use of opioid products. Patients often are reluctant to report pain because they may view the pain as a necessary part of their illnesses or surgeries. Proper education and knowledge on the part of providers, pharmacists and patients can improve significantly the management of pain.

One of the most important educational concepts is learning about the risks of addiction and, more specifically, what addiction is and isn't. It is well known that opioids carry the risk of addiction, the certainty of dependence with chronic use and the possibility of tolerance. However, these should not be reasons why proper pain management cannot be achieved.

Dependence to a medication means that the person is physiologically dependent on the medication and will suffer from withdrawal if the medication is stopped abruptly. Dependence can develop with many medications. For example, a patient taking a beta-blocker for hypertension for a period of time is physiologically dependent to the beta-blocker. Abrupt cessation can result in a rebound hypertension, which would signify a withdrawal symptom to the beta-blocker. Dependence to an opioid drug is nearly universal when the medication is used for longer than seven days to 10 days. That does not mean the patient is addicted to the opioid; it only means that he will suffer from withdrawal if the medication is stopped abruptly.

> Pain is the most frequent reason why patients seek out health care.

Tolerance to a drug is a physiological acclimatization where the patient has less of a response to a given dose of the drug. Tolerance may occur with sustained opioid use. However, it is now understood that tolerance does not occur at the rate experts once thought. Tolerance is highly variable among individual patients and often is mistaken for a sign of addiction. Physical dependence and tolerance are distinctly different from addiction in that they are both physical adaptations by the body to the drug.

Addiction implies some psychological need and is significantly rare when opioids are used for pain control.[5] Understanding these distinctions can eliminate barriers, increase pain control and improve patient outcomes.

PAIN CLASSIFICATIONS

Pain can be divided into two types: acute and chronic. Chronic pain can be further divided into pain from an active disease (chronic malignant pain) and pain not due to active disease (chronic nonmalignant pain). Those types of pain are differentiated by their duration, pathology, biological value, psychological confounds, social effects and their treatment (Table 2).[6]

Distinction between acute and chronic pain relies on a single continuum of time. Some interval since the onset of the pain is used to designate the onset of acute pain or the transition point when acute pain becomes chronic. Traditionally the distinction between acute and chronic pain is set arbitrarily, with continuous pain being defined as that lasting longer than three months, six months or pain that extends beyond the expected time of healing.

Pain can be further classified based on its neurophysiologic origins in what is known as the etiology-based classification. There are two main etiologies of pain, nociceptive and neuropathic. Nociceptive pain arises when normal sensory nerve fibers are stimulated by a noxious stimulus. Nociceptive pain can be subdivided further based on the tissue of origin into either somatic or visceral pains. Somatic pain arises from activation of nociceptors in the body structures, such as skin, bones, muscle and other connective tissues. Visceral pain arises from activation of nociceptors from deep inside the body, such as the internal organs of the abdominal and thoracic cavities. Neuropathic pain is pain caused by damage to the central or peripheral nervous systems resulting in abnormal transmission and/or processing of sensory information.

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ASSESSMENT OF PAIN

The most common reason for unrelieved pain is the failure of health care providers to ask routinely about pain and pain relief. It is important to incorporate routine pain assessment with practice. Multiple organizations have cultivated awareness about the poor management of pain and have succeeded in developing standards and guidelines for the management of pain. The Joint Commission on Accreditation of Health Care Organizations (JCAHO) developed standards for the assessment and treatment of pain that became effective January 2001. Other guidelines developed by the U.S. government, the American Pain Society and the World Health Organization are available to help practitioners improve pain care through regular assessment.[3]

Pain is subjective; there are no tests that can measure it. Objective signs of pain can be useful, especially in acute pain, but often are not present in chronic pain. The simplest way patients can communicate about their pain is by using a pain intensity rating scale. There are various pain intensity scales available, and a scale should be chosen based on an individual patient's needs and abilities. The pain intensity scale used most commonly is the numerical rating scale, which asks patients to rate the severity of their pain on a scale of one to 10. Another common scale used in children or elderly patients is the faces scale. Examples of various scales can be seen in Figure 1. It is important to remember that these scales are only as useful as the explanation that accompanies them. Patients should be given a short definition of what the scale is and how it should be used. For example, when using the numerical rating scale, patients should be instructed as follows: "On a scale of zero to 10, with 10 being the worst imaginable pain and zero being no pain, what is your pain rating *today*?" Routinely asking patients about their pain helps identify the effectiveness of the implemented therapy. Pain should be assessed regularly with every patient encounter and with every medication change.

TABLE 2

Differentiating types of pain*

	Acute	Chronic malignant	Chronic nonmalignant
Duration	Hours-days	Months-years	Unpredictable
Pathology	Present	Usually present	Often none found
Psychological confounds	Uncommon	Many (i.e., depression, loss of control)	Many (i.e., depression, anxiety, sleep disorder)
Biological value	High	Low	Low or absent
Social effects	Minimal	Variable—usually marked	Profound
Treatment	Primarily analgesics	Multimodal	Multimodal

Adapted from reference 6

TABLE 1

Reported barriers to pain management*

1. Barriers to pain management related to health care providers:

- Risk of disciplinary action by federal or state regulators
- Fear that prescribing, dispensing and administering drugs will lead to addiction
- Avoidance of pain patients due to difficulties and frustrations inherent in certain types of pain management
- Fear of being duped by drug seekers or being labeled as a "prescription doctor"
- *Lack of awareness of the extent to which pain can be managed with opioid analgesics*
- Inability to differentiate between and understand the risks of physical dependence and addiction resulting from use of opioids
- Concerns of excessive side effects from opioids
- Longstanding, yet invalid belief that patients are poor judges of the scope and severity of pain
- Conventional thoughts that pain medication should be reserved for patients with moderate-to-severe pain only
- Failure to re-evaluate patients' pain status
- Perpetuation of the outdated mechanistic model that characterizes pain as a neurophysiological response to disease
- Inadequate education regarding pathophysiology of acute and chronic pain, undertraining in most aspects of palliative care and clinical pharmacology of opioids and their utilization for particular patients with particular pain states
- Cross-training of practitioners and sharing of knowledge bases are exceptions rather than the rule

2. Barriers to pain management related to the health care and legal/regulatory systems:

- Hospitals operate on a disease-oriented model that discourages pain management or innovations that would improve pain management
- Pressure to reduce costs by denying potentially expensive treatments to terminally ill patients
- Inadequate coordination of care for seriously ill and terminally ill unless in a hospice setting
- Reimbursement policies of insurers centering on assumptions of "medical necessity" have resulted in irregular coverage of pain treatments
- Malpractice insurance policies that create disincentives for the practice of pain medicine
- *Limited stock of opioids due to concerns of possible abuse or diversion*
- Closed system of accountability that requires registration, record keeping and enforcement that allows regulating agencies to identify manufactures, distributors, physicians and pharmacists who may divert controlled substances for illicit use
- Federal and state controlled-substance laws and policies that restrict access to and the amount of opioids that can be prescribed in a set period to specific numbers of dosage units
- Prescribing of Schedule II drugs: drugs with high potential for abuse (most opioid analgesics) are the most carefully scrutinized by the Drug Enforcement Agency (DEA)
- Duplicate copy prescriptions required by some state regulators to prescribe Schedule II drugs are cumbersome to complete and frequently are unavailable in clinical practice settings
- Regulatory boards presenting aggregate numbers of disciplinary actions involving prescribing without differentiating among causes (example: indiscriminate prescribing, self-prescribing, diversion and overprescribing all presented together)

3. Barriers to pain management related to patients and/or family members:

- Ideology that pain builds character
- Fear to discuss pain and death in general
- Desire to be a "good patient" resulting in underreporting of pain, not wanting to distract physician from treating the disease process, not wishing to admit increasing pain that may be suggestive of disease progression
- Opiophobia, or generalized fear of taking medications, including legitimate use of analgesic medications
- Thought that admitting to pain and taking opioids to relieve pain are signs of personal weakness
- Belief that opioid analgesics will cause mental confusion, disorientation, personality change and drug-seeking behaviors
- Fear that use of opioid analgesics will lead family and friends to view patients as "druggies"
- Concern that in terminally ill patients that high doses of analgesics will lead to death, and family members may fear appearing *guilty of euthanasia*

Adapted from reference 4

ROLE OF OPIOIDS

In an attempt to improve pain management, the World Health Organization developed a Three-Step Analgesic Ladder. The three-step approach was developed as a guide to improve the treatment of pain and has become the gold standard for acute pain management in many settings. The ladder promotes a stepwise approach to the management of pain (Figure 2). The first step in the ladder states that for mild pain a nonopioid, such aspirin, acetaminophen or other NSAIDs, would be appropriate treatment. If pain is moderate, a combination opioid product, such as hydrocodone/apap, oxycodone/apap and codeine/apap, would be suitable. The top of the ladder states that for moderate to severe pain, a strong opioid, such as morphine, oxycodone or hydromorphone, would be fitting. In step three, opioids should be titrated to effect. At any level of the ladder, an adjuvant analgesic can be added in conjunction with the other analgesics to treat a specific type of pain, such as neuropathic pain.[8] The ladder was developed as a guide; application to patients still should be individualized.

The key principle to how fast and how much an opioid dose can be increased is determined by the severity of the pain. The dose can be increased by a percentage of the current dose, depending on the severity of the patient's pain rating. For moderate to

severe pain, the total daily opioid dose may be increased by 50 percent to 100 percent. For mild to moderate pain, the total daily opioid dose may be increased by 25 percent to 50 percent. An increase by less than 25 percent, under any circumstance, is likely to be clinically meaningless.[9]

It is widely appreciated that patients can demonstrate highly variable responses to different opioid drugs. That notion is the basis for rotation of opioids, a common practice among pain specialists. After titration of the opioid, rotation should take place if a patient has failed to achieve optimal analgesic benefit and is experiencing opioid-induced side effects. A trial of a different opioid may allow the patient to achieve analgesia with fewer incidences of side effects.

EQUIANALGESIC DOSING

Opioid rotation is just one of the reasons equivalent doses of opioid analgesics may need to be calculated. A change in the route of administration also necessitates the equianalgesic calculation of opioids. An important role of the pharmacist can be to provide providers with and verify equianalgesic dosing. There are many references available that provide equianalgesic tables. Variances among equianalgesic tables often lead to confusion. An equianalgesic table (Table 3) provides relative potency for various opioids and is a guide when making changes among opioids. It is important to remember that these tables are to be used only as a guide. Initial calculations should be completed and double checked, and the opioid should be converted to the new drug and dose. Then the patient should be re-evaluated using accepted pain assessment tools and techniques.

There are several accepted ways of calculating equianalgesic doses using the various tables available. Probably the oldest method of calculation is using morphine equivalents. That method is effective and often referenced in the literature and drug potency studies. Equianalgesic tables provide relative potencies for various opioids. Calculating the dose of the desired drug is completed using the total daily dose of the current drug and the listed potency ratio.

Opioid conversions can be approached like a simple math problem. First the patient's total 24-hour consumption of the opioid should be calculated. Second, if not already done, a different opioid should be chosen for pain control. Third, the equianalgesic table should be used to determine the equianalgesic ratio needed for conversion for the current drug and the desired new drug. Fourth, the multiplication should be completed, accounting for any change in units. Finally, the calculated dose should be rounded to the nearest available dosage strength.

Once again the equianalgesic tables are not exact. It is important that the patient be re-evaluated after he or she has been converted to the desired drug to see if the new drug and dose is effective. Titration of the new drug is completed using the guidelines discussed above based on the severity of the patient's pain.

PATIENT SCENARIO 1

Mr. Howard has been diagnosed with cancer. His physician asks him if he is experiencing any pain. Mr. Howard sort of shrugs his shoulders and says, "Yeah, some." Seeking more information, the physician asks Mr. Howard to rate his pain on a 10-point scale, with one being no pain and 10 being the worst possible pain. Mr. Howard thinks for a second and responds, "eight." What does this example demonstrate about how people communicate the extent to which they are in pain?

Answer

The reasons why people hesitate to communicate that they are in pain are many and varied. With this in mind it is essential that health care providers use intensity scales to gain an understanding of the degree of pain being experienced.

TABLE 3

Opioid equianalgesic table*

Opioid	po	Parenteral
Morphine	30	10
Codeine	200	130
Oxycodone	20	–
Hydrocodone	20–30	–
Hydromorphone	7.5	1.5
Fentanyl	–	0.1
Meperidine	300	75
Methadone**		

*Adapted from from: Gammaitoni AR, et al. Clinical Application of Opioid Equianalgesic Data. Clin J Pain. 2003;19(5):286-297

**See Table 4

METHADONE

Methadone is a synthetic opioid structurally classified as a diphenylheptane opioid analgesic. Methadone was discovered originally by a German laboratory during World War II, but it was not used as an analgesic until after the war was over. In the 1950s the U.S. Public Health Service hospitals recognized and used methadone as a treatment in opioid abstinence syndromes. Shortly thereafter, methadone grew in popularity for the treatment of heroin addictions as it was discovered that it prevented cravings and withdrawal symptoms in heroin users. In the early 1970s, strict legislation was passed regulating the prescribing or dispensing of methadone to physicians and pharmacies that had special registrations, thus the development of specialized methadone maintenance clinics. In the mid 1970s, the American Pharmaceutical Association (APhA) successfully sued for the ability to dispense methadone as an analgesic without special licenses and registration. The use of methadone to treat heroin addiction still is tightly regulated, requiring special licensure and registration for this purpose, but when dispensed as an analgesic, methadone does not require these special licenses and registration.[10]

Our current knowledge on the use of methadone as an analgesic is largely based on the experience with methadone in preventing opioid withdrawals in methadone maintenance clinics. Early use of methadone as an analgesic proved to be difficult, and several key differences were noted when comparing its use for maintaining abstinence versus analgesia. When methadone is used as an analgesic, it provides several distinct advantages compared with other opioids: namely, the drug has an inherently long half-life; it is highly potent; and it is inexpensive. The following discussion on methadone will review some of the characteristics of methadone that make it different from the other opioids, as well as special precautions that should be noted when using methadone.

Understanding the pharmacokinetic properties of methadone is vitally important to understanding how it is to be used as an analgesic. Methadone is highly bioavailable and lipophilic, resulting in wide distribution and rapid onset of action of the drug. Methadone analgesia generally begins within an hour or two of administration. Methadone is inherently long acting; the half-life of methadone can range between 22 and 28 hours. Methadone is metabolized by the liver to inactive metabolites through the cytochrome p450 enzyme system as a major substrate of the 3A4 enzyme pathway and a minor substrate of the 2D6 enzyme pathway. Interestingly, methadone also is a weak enzyme inhibitor of the 3A4 p450 enzymes and a moderate

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FIGURE 1

Examples of pain intensity scales

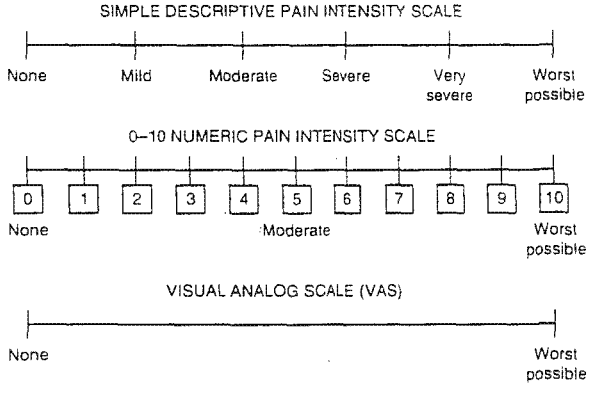
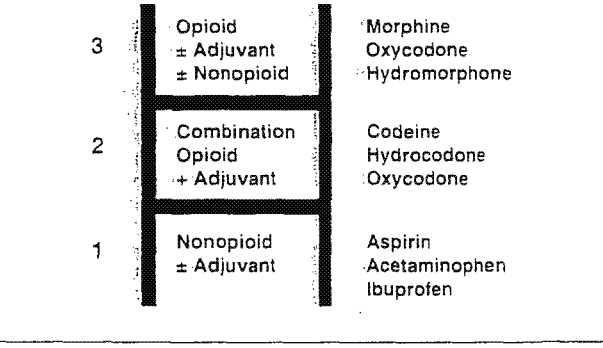


FIGURE 2

WHO analgesic ladder



Pharmacist pain management: a focus on opioids and conversion issues

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inhibitor of the 2D6 p450 enzymes, leading to the possibility of some auto-inhibition.[11] Careful notation of concomitant drugs that either increase or decrease the p450 metabolic pathways is important to prevent potential drug-drug interactions. That is specifically important because there have been recent reports of patients taking high dose methadone, generally greater than 200 mg/day, that have noted QT prolongation and development of cardiac arrhythmias such as Torsades de Pointes.[12-15] Careful monitoring for the p450 drug-drug interactions, as well as for any other drug-drug that may result in cardiac conduction problems is important. The inactivated methadone metabolites then are excreted renally.

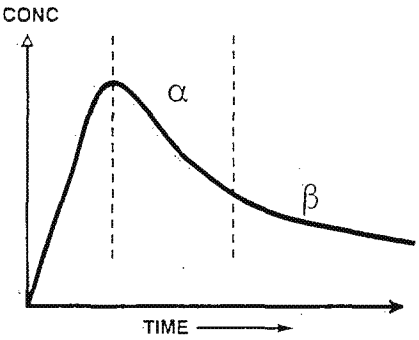
In the case of opioid abstinence, it long has been known that once-daily dosing is adequate to prevent withdrawals and cravings. Dosing in pain management is different. Methadone's analgesic properties do not appear to last as long as the drug's detectable half-life. The duration of analgesia for methadone appears to be between four hours to six hours with acute dosing, and then increases to between eight hours to 10 hours with chronic repeated dosing. When dosing methadone for analgesic effects, six-hour to eight-hour dosing intervals generally are needed to maintain stable analgesic control.

There are several thoughts as to why the duration of analgesia of methadone is shorter than its half-life: one is based on the fact that methadone has a biphasic elimination curve,[16] and another is that methadone may dissociate rapidly and readily from the opioid receptors.

Methadone's elimination has two distinct phases called the alpha-elimination phase and the beta-elimination phase (Figure 3). The alpha-elimination is considered to be a more rapid elimination, and the elimination curve is steeper. The beta-elimination is considered to be slower, and the elimination curve flattens out significantly compared with the alpha-phase. The alpha-elimination phase lasts until about six hours to eight hours after dosing.

FIGURE 3

Biphasic methadone elimination



PICTORIAL PAIN ASSESSMENT SCALE

PATIENT SCENARIO 2

A physician calls regarding a patient who is currently taking morphine sustained-release 30 mg po TID and he wants to convert him to oxycodone. He would like you, as the pharmacist, to help determine the equianalgesic dose.

Answer:

1) Total 24-hour consumption of morphine = 90 mg
2) Provider wants to change to oxycodone
3) Equianalgesic ratio: morphine 30 mg = oxycodone 20 mg
4) Complete multiplication and solve for x:

90 mg morphine / x

30 mg morphine / 20 mg oxycodone; x = 60 mg of oxycodone

5) Oxycodone extended-release is available in 20 mg tablets so there is no need to round. Recommend 20 mg po q 8 hours.

PATIENT SCENARIO 3

A local physician calls regarding a patient who currently is taking sustained-release oxycodone 80 mg po q 8 hours. Because of financial reasons, the physician is considering switching the patient to methadone. He would like you, as a pharmacist, to help determine the equianalgesic dose.

Answer:

1) Total 24-hour consumption of morphine equivalents:
   - Total daily oxycodone = 240 mg
   - Equianalgesic ratio: morphine 30 mg = oxycodone 20 mg
   - Calculate total daily morphine equivalents:

240 mg oxycodone / x

20 mg oxycodone / 30 mg morphine; x = 360 mg of po morphine

2) Provider wants to change to methadone
3) Equianalgesic ratio for morphine 300-1,000 mg use methadone:
   1 mg = morphine 12 mg
4) Complete multiplication and solve for x

360 mg morphine / x

12 mg morphine / 1 mg methadone; x = 30 mg of methadone

5) Methadone is available in 10 mg tablets so there is no need to round. Recommend 10 mg po q 8 hours.

After that, elimination begins to slow as it enters the beta-phase, which can last up to 30 hours.[16] The change in elimination rate coincides with the observed duration of analgesia for methadone. As the methadone enters its beta-elimination, the drug may not continue to bind to the opioid receptors and, thus, as it dissociates more readily, analgesia is not maintained. The differences in the elimination phases may help explain why methadone lasts for roughly 24 hours for the prevention of withdrawals and cravings in the treatment of heroin addiction, but the analgesia only lasts for a fraction of that time.

Chemically, methadone is available only as a racemic mixture of equal portions of dextrorotatory (*d*) and levorotary (*l*) isomers. The *d* isomer is relatively inactive as an opioid analgesic as the *l* isomer is roughly eight times to 50 times more potent than the *d* isomer in terms of analgesic effect.[16] The *d* isomer, though it has little opioid-mediated analgesic properties, is not devoid of any effect. The *d* isomer is a relatively potent n-methyl-d-aspartate receptor (NMDA) antagonist,[17] a unique activity compared with the other opioid analgesics. The NMDA receptor has been implicated in several divergent activities related to pain transmission and analgesia, including, but not limited to, neuropathic pain signal transmission, the wind-up phenomenon (pain amplification due to central nervous system sensitization to pain signals) and development of tolerance to opioid analgesics.[18-21] Although the specific actions of the NMDA receptor in pain are not clearly elucidated and actually may be multifactorial, the NMDA receptor an-

TABLE 4

Determining the conversion ratio for methadone, based on current morphine equivalent dose

Oral morphine equivalent dose	Conversion ratio (morphine : methadone)
less than 100 mg	1 : 4
100–300 mg	1 : 8
300–1,000 mg	1 : 12
> 1,000 mg	1 : 20

PRACTICE POINTS

1. Signs or symptoms of physical dependence and/or tolerance to an opioid analgesic do not mean the patient is an addict.
2. Pain assessment is helpful to determine classification of patient's pain.
3. Opioid equianalgesic tables do not provide absolute ratios; they are a rough equivalency between opioid doses. Dose titration or tapering may be necessary based on patient response following the conversion using opioid equianalgesic tables.
4. Methadone equivalency ratios may change based on previous opioid dose being calculated in morphine equivalents.
5. Double-check all calculations and equivalency ratios.

tagonism effects of methadone can be interpreted as a positive effect.

Methadone does not reach steady state for several days to weeks because of its inherently long half-life, its potential for p450 enzymatic drug interactions and the beta-elimination curve. When methadone is dosed for analgesia, subsequent doses are administered well before all of the drug from previous doses has been eliminated from the body. Careful equivalent dosing calculations are necessary to avoid accidental rapid drug accumulation and potential overdose within the first few days after the drug has been started. Dose titration should be done slowly, giving several days to weeks between titrations.

Methadone's potency as an analgesic has been widely underestimated. Early single-dose potency equivalency trials comparing methadone with morphine in opioid-naive subjects resulted in calculated equivalent ratios of 1:2 to 1:4.[22] In patients with chronic pain who are opioid tolerant, the equivalencies may be much greater, especially for patients who use higher daily doses of morphine equivalents. Recent studies have begun to show that the higher the equivalent dose of morphine a patient is using, the more sensitive he might be to methadone, necessitating larger equivalency ratios.[22,23] That may be because of an increasingly incomplete cross-tolerance between the drugs as a patient becomes more tolerant to higher doses of morphine, or it may be that the additional NMDA-receptor antagonism is more pronounced once a patient has become more tolerant to the opioid analgesic effects. Whatever the cause for the difference between the equianalgesic ratios between other opioids and methadone, the result is that there is a greater risk of opioid overdose due to increased sensitivity to methadone's effects.

When converting an opioid dose to methadone from another opioid analgesic, a conversion to the equivalent total daily dose of oral morphine is recommended first. Calculating the equivalent methadone dose then can be done using equivalency ratios based on the daily consumption of morphine equivalents.[22,23] When the previous daily dose of oral morphine equivalents is less than 100 mg, calculate using a ratio of 1 mg of oral methadone to 4 mg of oral morphine. When the previous daily dose of oral morphine equivalents is between 100 mg and 300 mg, calculate using a ratio of 1 mg of oral methadone to 8 mg of oral morphine. When the previous daily dose of oral morphine equivalents is between 300 mg and 1,000 mg, calculate using a ratio of 1 mg of oral methadone to 12 mg of oral morphine. When the previous daily dose of oral morphine equivalents is greater than 1,000 mg, calculate using a ratio 1 mg of oral methadone to 20 mg of oral morphine (Table 4).

Unfortunately, that sliding scale equivalency ratio is not well defined, and there are many variations available in the literature. As a result, there have been many different models for opioid rotation/titration developed for methadone (Table 5). Also very important to note is the fact that the equianalgesic conversion ratios aren't necessarily bidirectional. Thus, once a patient is titrated to a stable methadone dose, it may be difficult to determine the equivalency of other opioid agents if further change is necessitated.

Methadone is a potent, long-acting, inexpensive opioid analgesic with a clean metabolism profile, (i.e., no active metabolites), but it needs to be managed carefully. The drug's propensity for accumulation, complexity in determining equivalency and potential for drug-drug interactions, as well as and the potential for development of opioid-induced side effects, make the drug difficult to manage for practitioners unless they understand its kinetics and are well versed in its analgesic effects.

TABLE 5

Titration models for methadone

Edmonton Model	*For opioid tolerant patients ...* Recommend a 3-day conversion protocol of oral/parenteral MS equivalent to oral ME. Decrease MS equivalent by ~33% and increase equivalent ME by ~33% each day using a MS:po ME dosing ratio of 10:1
Italian Model	*For opioid-naive or tolerant patients ...* Schedule based on MS or equivalent opioid. Opioid naive: start ME 3 mg q8h MS dose ≤ 60 mg po/day: switch to ME 5 mg q8h. MS dose 70 – 90 mg po/day: switch to ME at 25% of 24h MS dose. MS dose ≥ 100 mg po/day: switch to ME at 1/6 or 15% of 24h MS dose. The dose of methadone is titrated each day until pain relief is obtained w/o side effects.
British Model	*For opioid tolerant patients ...* Recommend a 6-day conversion protocol oral morphine (MS) equivalent to oral methadone (ME): 1. Stop current opioid • DAY 1–5: If current oral MS equivalent is ≤ 300 mg/day, dose ME at fixed dose equal to 10% of MS equivalent. OR If current oral MS equivalent is > 300 mg/day, dose ME at a max fixed dose of 30 mg q3h. • DAY 6: Average the amount of daily methadone taken on days 4 & 5 and convert to a q12h dosing. Increase the scheduled methadone dose by 30–50% every 4–6 days based on pm use.
German Model	*Opioid-tolerant patients* using ≥ 600 mg/day of morphine or equivalent opioid: DAY 1: Stop MS, initiate ME 5–10 mg po q4h, and q1h prn. DAYS 2–3: If no pain control: ME up to 30% q4h and q1h prn to pain relief and no AE's. DAY 4: After 72h change to q8h and q3h prn at the same single dose used during days 2–3. ≥ DAY 5: If no pain control: ME up to 30% q8h and q3h prn until sufficient pain relief and no AE's. *(Note: Dose of methadone may range from 10–200 mg q8h.)*
Chinese Model	*Utilized an ad libitum dosing schedule to convert oral MS to oral ME in 37 patients.* DAY 1: Stop current morphine dose. Convert total daily MS dose to po ME using a MS:ME ratio of 12:1 up to a max fixed dose of 30 mg q3h, prn. Follow up: Ad libitum dosing continued until demand for methadone was ↓ or stabilized. Total daily dose of ME required was divided by 2 or 3 and administered q8h or q12h. Daily ME dose increased by 50% if pain uncontrolled by day 7.

CONCLUSION

Pharmacists can play a pivotal role in the management of patients with pain. Education regarding the differences between dependence, tolerance and addiction is a key first step. Development of standards and guidelines for the practice of pain management has improved the recognition of the importance of pain management. Assessment of the patient's pain by health care providers—including pharmacists—is important in recognition, classification and evaluation of pain. Identi-

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Pharmacist pain management: a focus on opioids and conversion issues

CONTINUED FROM PAGE 19

fying the types of pain a patient may be experiencing better enables the pharmacist to recommend specific treatment options. Specific understanding of dosing, kinetics, titration and rotation of opioids in pain management is where pharmacists can help direct patient care and improve outcomes. Methadone, compared with the other opioid analgesics, possesses many unique characteristics that are not understood by many in the health care community. In terms of safety and patient monitoring, pharmacists' knowledge and understanding of those characteristics are vital in methadone's use as an analgesic. In conclusion, opioid analgesics can be highly effective in the management of pain when dosed, administered and monitored properly.

For a complete list of references, visit www.drugstorenews.com.

Learning Assessment

Successful completion of "Pharmacist pain management: a focus on opioids and conversion issues" (lesson 401-000-05-009-H01) is worth two contact hours of credit. Mail completed answer sheet to *DrSN/CE Quarterly*, P.O. Box 31180, Tampa, FL 33631-3180. For faster service, fax to (813) 626-7203. For fastest service, visit our Web site at www.drugstorenews.com.

1. Lost productivity from common pain is estimated to cost approximately $_____ billion each year.
   a. 100
   b. 74
   c. 61
   d. 53

2. An example of a health care provider barrier to effective pain management is/are
   a. a patient's desire to be a good patient.
   b. failure to re-evaluate patients' pain status..
   c. insurers' reimbursement policies.
   d. regulatory restrictions on the amount of opioids that may be prescribed in a period of time.

3. An example of patient or family member barrier to effective pain management is
   a. risk of disciplinary action by federal or state regulators.
   b. fear of being duped by drug seekers.
   c. limited stock of opioids because of concerns of possible abuse or diversion.
   d. fear that any use of opioids with lead to becoming an addict.

4. Tolerance to opioids
   a. means a person is physiologically dependent on the medication and will suffer from withdrawal if the medication is stopped abruptly.
   b. means a physiological acclimatization where the patient has less of a response to a given dose of the drug.
   c. implies some psychological need.

5. Dependence
   a. means a person is physiologically dependent on the medication and will suffer from withdrawal if the medication is stopped abruptly.
   b. means a physiological acclimatization where the patient has less of a response to a given dose of the drug.
   c. implies some psychological need.

6. Addiction
   a. Means a person is physiologically dependent on the medication and will suffer from withdrawal if the medication is stopped abruptly.
   b. Means a physiological acclimatization where the patient has less of a response to a given dose of the drug.
   c. implies some psychological need.

7. Objective signs of pain often are not present in chronic pain.
   a. True
   b. False

8. One advantage of pain scales is that there is no need to explain them to the patient.
   a. true
   b. false

9. According to the WHO Analgesic ladder, treatment of all pain patients should begin at step one, with aspirin, acetaminophen or other NSAIDs.
   a. true
   b. false

10. When increasing opioids dosage, which of the following would be appropriate?
    a. A patient with moderate pain has his or her opioid dosage increased by 20 percent.
    b. A patient with severe pain has his or her opioid dosage increased by 200 percent.
    c. A patient with mild pain has his or her opioid dosage increased by 75 percent.
    d. A patient with moderate pain has his or her opioid dosage increased by 50 percent.

11. Patients often demonstrate highly variable responses to different opioid drugs.
    a. true
    b. false

12. The regulations, licensure and registrations required to dispense methadone for the treatment of pain are the same as those for treatment of heroin addition.
    a. true
    b. false

13. Characteristics of methadone that are advantageous in the treatment of pain include
    a. its long half-life.
    b. the fact that it is highly potent.
    c. the fact that it is inexpensive.
    d. all of the above.

14. When used in the treatment of pain, multiple daily doses are required.
    a. true
    b. false

15. With methadone, steady state may not be reached until after _____
    a. four doses to six doses.
    b. two days to three days.
    c. one week.
    d. several weeks.

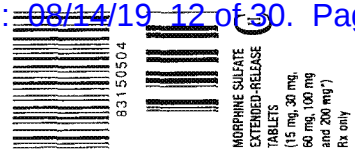
16. The ratio for calculating an equianalgesic dose of methadone will vary depending on
    a. the patient's body weight.
    b. the patient's gender.
    c. the patient's previous daily dose of oral morphine equivalents.
    d. the length of time over which the patient has been receiving opioid treatment.

17. Equianalgesic conversion ratios are bidirectional, thus enabling precise calculation of the appropriate dose when changing between any opioid agents.
    a. true
    b. false

18. Mr. Downs suffers from chronic back pain. He comes into your pharmacy for a refill of his oxycodone prescription. As you are ringing up his prescription you ask him how he's feeling and how his pain is. He responds, "OK, I guess." You wish him a good day and he leaves.
    a. It was inappropriate for you to ask about his pain. That is between him and his physician.
    b. Well done. You have assessed his pain effectively.
    c. Good start, but you should have followed up by asking him to rate his pain on a pain intensity scale

19. In the process of converting oxycodone, 40 mg po q8hrs, to methadone, the appropriate oral morphine to methadone ratio would be
    a. 1:4.
    b. 1:8.
    c. 1:12.
    d. 1:20.

20. With regard to methadone:
    a. the analgesic effect does not last as long as the drug's detectable half-life.
    b. the duration of analgesic effect increased from four hours to six hours with acute dosing to eight hours to 10 hours with chronic repeated dosing.
    c. drugs that increase or decrease the p450 metabolic pathways may result in drug interactions with methadone.
    d. all of the above



Morphine Sulfate Extended-Release Tablets

15 mg, 30 mg, 60 mg, 100 mg and 200 mg*

Rx only

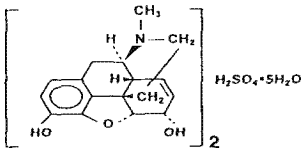
C II

*200 mg for use in opioid-tolerant patients only

DESCRIPTION

Morphine Sulfate Extended-Release Tablets are supplied in tablet form for oral administration.

Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate and has the following structural formula:



$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ MW = 758.83

Each Morphine Sulfate Extended-Release Tablet, 15 mg contains: 15 mg Morphine sulfate USP. Inactive ingredients: hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, polyethylene glycol NF, polydextrose FCC , silicone dioxide NF, titanium dioxide USP, triacetine USP, FD&C Blue No. 2.

Each Morphine Sulfate Extended-Release Tablet, 30 mg contains: 30 mg Morphine sulfate USP. Inactive ingredients: hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, polyethylene glycol NF, polydextrose FCC, silicone dioxide NF, titanium dioxide USP, triacetine USP, FD&C Blue No. 2, D&C Red No. 7.

Each *Morphine Sulfate Extended-Release Tablet, 60 mg contains: 60 mg Morphine sulfate USP. Inactive ingredients: hydroxypropyl* methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, polyethylene glycol NF, polydextrose FCC, silicone dioxide NF, titanium dioxide USP, triacetine USP, FD&C Yellow No. 6, iron oxide red NF.

Each Morphine Sulfate Extended-Release Tablet, 100 mg contains: 100 mg Morphine sulfate USP. Inactive ingredients: hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, silicone dioxide NF, titanium dioxide USP, triacetine USP, iron oxide black.

Morphine Sulfate Tablets (morphine sulfate extended-release tablets) 200 mg Tablets* (For use in opioid-tolerant patients only)

Each Morphine Sulfate Extended-Release Tablets, 200 mg* contains: 200 mg Morphine sulfate USP. Inactive ingredients: hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, polyethylene glycol NF, silicone *dioxide NF, titanium dioxide USP, triacetine USP, FD&C Blue No. 1, D&C Yellow No. 10 Lake.*

***FOR USE IN OPIOID-TOLERANT PATIENTS ONLY.**

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism

Morphine Sulfate Extended-Release Tablets are extended-release tablets containing morphine sulfate. Following oral administration of a given dose of morphine, the amount ultimately absorbed is essentially the same whether the source is Morphine Sulfate Extended-Release Tablets or a conventional formulation. Morphine is released from Morphine Sulfate Extended-Release *Tablets somewhat more slowly than from conventional oral preparations. Because of pre-systemic elimination (i.e., metabolism in* the gut wall and liver) only about 40% of the administered dose reaches the central compartment.

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Morphine also crosses the placental membranes and has been found in breast milk.

Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes, virtually all morphine is converted to glucuronide metabolites; among these, morphine-3-glucuronide is present in the highest plasma concentration following oral administration.

The glucuronide system has a very high capacity and is not easily saturated even in disease. Therefore, rate of delivery of morphine to the gut and liver should not influence the total and, probably, the relative quantities of the various metabolites formed. Moreover, even if rate affected the relative amounts of each metabolite formed, it should be unimportant clinically because morphine's metabolites are ordinarily inactive.

The following pharmacokinetic parameters show considerable inter-subject variation but are representative of average values reported in the literature. The volume of distribution (Vd) for morphine is 4 liters per kilogram, and its terminal elimination half-life is normally 2 to 4 hours.

Following the administration of conventional oral morphine products, approximately fifty percent of the morphine that will reach the central compartment intact reaches it within 30 minutes. Following the administration of an equal amount of Morphine Sulfate Extended-Release Tablets to normal volunteers, however, this extent of absorption occurs, on average, after 1.5 hours.

The possible effect of food upon the systemic bioavailability of Morphine Sulfate Extended-Release Tablets has not been systematically evaluated for all strengths. Data from at least one study suggests that concurrent administration of Morphine Sulfate Extended-Release Tablets with a fatty meal may cause a slight decrease in peak plasma concentration.

Variation in the physical/mechanical properties of a formulation of an oral morphine drug product can affect both its absolute bioavailability and its absorption rate constant (k_a). The formulation employed in Morphine Sulfate Extended-Release Tablets has not been shown to affect morphine's oral bioavailability, but does decrease its apparent k_a. Other basic pharmacokinetic parameters (e.g., volume of distribution [Vd], elimination rate constant [k_e], clearance [Cl]) are unchanged as they are fundamental properties of morphine in the organism. *However, in chronic use, the possibility that shifts in metabolite to parent drug ratios may occur cannot* be excluded.

When immediate-release oral morphine or Morphine Sulfate Extended-Release Tablets is given on a fixed dosing regimen, steady-state is achieved in about a day.

For a given dose and dosing interval, the AUC and average blood concentration of morphine at steady-state (Css) will be independent of the specific type of oral formulation administered so long as the formulations have the same absolute bioavailability. The absorption rate of a formulation will, however, affect the maximum (C_{max}) and minimum (C_{min}) blood levels and the times of their occurrence.

Pharmacodynamics

The effects described below are common to all morphine-containing products.

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis).

The precise mechanism of the analgesic action is unknown. However, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia.

Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an *increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive* contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of sphincter of Oddi.

Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

Plasma Level-Analgesia Relationships

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose. In non-tolerant individuals, plasma morphine concentration-efficacy relationships have been demonstrated and suggest that opiate receptors occupy effector compartments, leading to a lag-time, or hysteresis, between rapid changes in plasma morphine concentrations and the effects of such changes. The most direct and predictable concentration-effect relationships can, therefore, be expected at distribution equilibrium and/or steady-state conditions. In general, the minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately 5 to 20 ng/mL.

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naive individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

For any fixed dose and dosing interval, Morphine Sulfate Extended-Release Tablets will have at steady-state, a lower C_{max} and a higher C_{min} than conventional morphine. This is a potential advantage; a reduced fluctuation in morphine concentration during the dosing interval should keep morphine blood levels more centered within the theoretical "therapeutic window." (Fluctuation for a dosing interval is defined as $[C_{max}\text{-}C_{min}]/[Css\text{-}average]$.) On the other hand, the degree of fluctuation in serum morphine concentration might conceivably affect other phenomena. For example, reduced fluctuations in blood morphine concentrations might influence the rate of tolerance induction.

The elimination of morphine occurs primarily as renal excretion of 3-morphine glucuronide. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling. Because morphine is primarily metabolized to inactive metabolites, the effects of renal disease on morphine's elimination are not likely to be pronounced. However, as with any *drug, caution should be taken to guard against unanticipated accumulation if renal and/or hepatic function is seriously impaired.*

INDICATIONS AND USAGE

Morphine Sulfate Extended-Release Tablets are an extended-release oral morphine formulation indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.

The morphine sulfate extended-release tablets 200 mg strength is a high dose, extended-release, oral morphine formulation indicated for the relief of pain in opioid-tolerant patients only.

CONTRAINDICATIONS

Morphine Sulfate Extended-Release Tablets are contraindicated in patients with known hypersensitivity to the drug, in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

Morphine Sulfate Extended-Release Tablets are contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS (See also: CLINICAL PHARMACOLOGY)

Impaired Respiration

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in the elderly and debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or pre-existing increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head injuries.

Hypotensive Effect

Morphine Sulfate Extended-Release Tablets, like all opioid analgesics, may cause severe hypotension in an individual whose ability *to maintain his blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs* such as phenothiazines or general anesthetics. (See also: PRECAUTIONS; Drug Interactions.) Morphine Sulfate Extended-Release Tablets may produce orthostatic hypotension in ambulatory patients.

Morphine Sulfate Extended-Release Tablets, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Interactions with other CNS Depressants

Morphine Sulfate Extended-Release Tablets, like all opioid analgesics, should be used with great caution and in reduced dosage in patients who are currently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

From a theoretical perspective, agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic. *In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.*

Drug Dependence

Morphine can produce drug dependence and has a potential for being abused. Tolerance as well as psychological and physical dependence may develop upon repeated administration. Physical dependence, however, is not of paramount importance in the management of terminally ill patients or any patients in severe pain. Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. After prolonged exposure to opioid analgesics, if withdrawal is necessary, it must be undertaken gradually. (See DRUG ABUSE AND DEPENDENCE.)

Infants born to mothers physically dependent on opioid analgesics may also be physically dependent and exhibit respiratory depression and withdrawal symptoms. (See DRUG ABUSE AND DEPENDENCE.)

Other

Although extremely rare, cases of anaphylaxis have been reported.

PRECAUTIONS (See also: CLINICAL PHARMACOLOGY)

Special precautions regarding Morphine Sulfate Extended-Release Tablets 200 mg Tablets

Morphine Sulfate Extended-Release Tablets 200 mg Tablets are for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. Care should be taken in its prescription and patients should be instructed against use by individuals other than the patient for whom it was prescribed, as this may have severe medical consequences for that individual.

General

Morphine Sulfate Extended-Release Tablets are intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The extended-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism.) However, Morphine Sulfate Extended-Release Tablets do not release morphine continuously over the course of a dosing interval. The administration of single doses of Morphine Sulfate Extended-Release Tablets on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of *morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater fluctuations in* morphine plasma level has not been systematically evaluated. (See DOSAGE AND ADMINISTRATION.)

As with any potent opioid, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to the selection of the initial dose and dosing interval of Morphine Sulfate Extended-Release Tablets, attention should be given to 1) the daily dose, potency, and characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist/antagonist), 2) the reliability of the relative potency estimate used to calculate the dose of morphine needed (N.B. potency estimates may vary with the route of administration), 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient.

Selection of patients for treatment with Morphine Sulfate Extended-Release Tablets should be governed by the same principles that apply to the use of morphine or other potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; kyphoscoliosis, or inability to swallow.

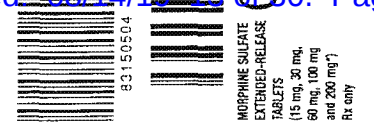
The administration of morphine, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Morphine may aggravate pre-existing convulsions in patients with convulsive disorders. Morphine should be used with caution in patients about to undergo surgery of the biliary tract *since it may cause spasm of the sphincter of Oddi. Similarly, morphine should* be used with caution in patients with acute pancreatitis secondary to biliary tract disease.

Information for Patients

If clinically advisable, patients receiving Morphine Sulfate Extended-Release Tablets should be given the following instructions by the physician:

1. Appropriate pain management requires changes in the dose to maintain best pain control. Patients should be advised of the need to contact their physician if pain control is inadequate, but not to change the dose of Morphine Sulfate Extended-*Release Tablets without consulting their physician.*
2. Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on Morphine Sulfate Extended-Release Tablets or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
3. Morphine should not be taken with alcohol or other CNS depressants (sleep aids, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other prescription medications are currently being used or are prescribed for future use.
4. For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted regarding analgesics and other drug use.
5. Upon completion of therapy, it may be appropriate to taper the morphine dose, rather than abruptly discontinue it.
6. *While psychological dependence ("addiction") to morphine used in the treatment of pain is very rare, morphine is one of a* class of drugs known to be abused and should be handled accordingly.
7. The Morphine Sulfate Extended-Release Tablets 200 mg Tablet is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. Special care must be taken to avoid accidental ingestion or the use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.



Drug Interactions (See also: **WARNINGS**)

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol may produce additive depressant effects. Respiratory depression, hypotension, and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including Morphine Sulfate Extended-Release tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy

Teratogenic Effects – CATEGORY C

Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in mates or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such *experience cannot exclude the possibility of infrequent or subtle damage to the human fetus.*

Morphine Sulfate Extended-Release Tablets should be used in pregnant women only when clearly needed. (See also: **PRECAUTIONS: Labor and Delivery**, and **DRUG ABUSE AND DEPENDENCE**.)

Nonteratogenic Effects

Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

Labor and Delivery

Morphine Sulfate Extended-Release Tablets are not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

Nursing Mothers

Low levels of *morphine* have been detected in the breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving Morphine Sulfate Extended-Release Tablets since morphine may be excreted in the milk.

Pediatric Use

Use of Morphine Sulfate Extended-Release Tablets have not been evaluated systematically in children.

Geriatric Use

Clinical studies of Morphine Sulfate Extended-Release Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

Most Frequently Observed

Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria and euphoria.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some *adverse reactions in ambulatory patients may be alleviated if the patient lies down.*

Less Frequently Observed Reactions

Central Nervous System: Weakness, headache, agitation, tremor, uncoordinated muscle movements, seizure, alterations of mood (nervousness, apprehension, depression, floating feelings), dreams, muscle rigidity, transient hallucinations and disorientation, visual disturbances, insomnia, increased intracranial pressure

Gastrointestinal: Dry mouth, biliary tract spasm, laryngospasm, anorexia, diarrhea, cramps, taste alterations, constipation, ileus, intestinal obstruction, increase in hepatic enzymes

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension, hypertension

Genitourinary: Urine retention or hesitance, reduced libido and/or potency

Dermatologic: Pruritus, urticaria, other skin rashes, edema, diaphoresis

Other: Antidiuretic effect, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia, miosis, anaphylaxis

DRUG ABUSE AND DEPENDENCE

Opioid analgesics may cause psychological and physical dependence (see **WARNINGS**). Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with narcotic antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, etc.; see also **OVERDOSAGE**). Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued narcotic usage. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and, subsequently, by decreases in the intensity of analgesia.

In chronic-pain patients, and in narcotic-tolerant cancer patients, the administration of Morphine Sulfate Extended-Release Tablets should be guided by the degree of tolerance manifested. Physical dependence, per se, is not ordinarily a concern when one is dealing with opioid-tolerant patients whose pain and suffering is associated with an irreversible illness.

If Morphine Sulfate Extended-Release Tablets are abruptly discontinued, a moderate to severe abstinence syndrome may occur. The opioid agonist abstinence syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep or "yen" and mydriasis during the first 24 hours. These symptoms often increase in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, twitching and spasms of muscles; kicking movements; severe backache, abdominal and leg pains; abdominal and muscle cramps; hot and cold flashes, insomnia; nausea, anorexia, *vomiting, intestinal spasm, diarrhea; coryza and repetitive sneezing; increase in body temperature,* blood pressure, respiratory rate and heart rate. Because of excessive loss of fluids through sweating, vomiting and diarrhea, there is usually marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse can occur. Without treatment most observable symptoms disappear in 5 to 14 days; however, there appears to be a phase of secondary or chronic abstinence which may last for 2 to 6 months characterized by insomnia, irritability, and muscular aches.

If treatment of physical dependence of patients on Morphine Sulfate Extended-Release Tablets is necessary, the patient may be detoxified by gradual reduction of the dosage. Gastrointestinal disturbances or dehydration should be treated accordingly.

OVERDOSAGE

Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, bradycardia, hypotension and death.

In the treatment of overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonist, naloxone, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2 mg) should be administered intravenously; however, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. If the response to naloxone is suboptimal or not sustained, additional naloxone may be administered, as needed, or given by continuous infusion to maintain alertness and respiratory function; however, there is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on Morphine Sulfate Extended-Release Tablets. In such cases, an abrupt or complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

Note: In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of a narcotic antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with care and by titration with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSAGE AND ADMINISTRATION

(See also: **CLINICAL PHARMACOLOGY, WARNINGS,** and **PRECAUTIONS** sections)

MORPHINE SULFATE EXTENDED-RELEASE TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED.

TAKING BROKEN, CHEWED OR CRUSHED MORPHINE SULFATE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

Morphine Sulfate Extended-Release Tablets are intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The extended-release nature of the formulation allows it to be administered on a more *convenient schedule than conventional immediate-release oral morphine products. (See* ***CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism***.) However, Morphine Sulfate Extended-Release Tablets do not release morphine continuously over the course of a dosing interval. The administration of single doses of Morphine Sulfate Extended-Release Tablets on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of greater fluctuations in morphine plasma level has not been systematically evaluated.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to enumerate every consideration that is important to selection of initial dose and dosing interval of Morphine Sulfate Extended-Release Tablets, attention should be given to 1) the daily dose, potency, and precise characteristics of the opioid the patient has been taking previously (e.g., whether it is a pure agonist or mixed agonist/antagonist), 2) the reliability of the relative potency estimate used to calculate the dose of morphine needed [N.B. potency estimates may vary with the route of administration], 3) the degree of opioid tolerance, if any, and 4) the general condition and medical status of the patient.

The following dosing recommendations, therefore, can only be considered suggested approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient.

Conversion from Conventional Oral Morphine to Morphine Sulfate Extended-Release Tablets

A patient's daily morphine requirement is established using immediate-release oral morphine (dosing every 4 to 6 hours). The patient is then converted to Morphine Sulfate Extended-Release Tablets in either of two ways: 1) by administering one-half of the patient's 24-hour requirement as Morphine Sulfate Extended-Release Tablets on an every 12-hour schedule; or, 2) by administering one-third of the patient's daily requirement as Morphine Sulfate Extended-Release Tablets on an every eight hour schedule. With either method, dose and dosing interval is then adjusted as needed (see discussion below). The 15 mg tablet should be used for *initial conversion for patients whose total daily requirement is expected to be less than 60 mg. The 30 mg tablet strength is* recommended for patients with a daily morphine requirement of 60 to 120 mg. When the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to Morphine Sulfate Extended-Release Tablets

Morphine Sulfate Extended-Release Tablets can be administered as the initial oral morphine drug product; in this case, however, particular care must be exercised in the conversion process. Because of uncertainty about, and intersubject variation in, relative estimates of opioid potency and cross tolerance, initial dosing regimens should be conservative; that is, an underestimation of the 24-hour oral morphine requirement is preferred to an overestimate. To this end, initial individual doses of Morphine Sulfate Extended-Release Tablets should be estimated conservatively. In patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day, the 30 mg tablet strength is recommended for the initial titration period. Once a stable dose regimen is reached, the patient can be converted to the 60 mg or 100 mg tablet strength, or an appropriate combination of tablet strengths, if desired.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and possibly, by an individual's medical condition. Consequently, it is difficult to recommend any fixed rule for converting a patient to Morphine Sulfate Extended-Release Tablets directly. The following general points should be considered, however.

1. ***Parenteral to oral morphine ratio:*** Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only three times the daily parenteral morphine requirement may be sufficient in chronic use settings.

2. **Other parenteral or oral opioids to oral morphine:** Because there is lack of systematic evidence bearing on these types of analgesic substitutions, specific recommendations are not possible.

Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In *general, it is safer to underestimate the daily dose of Morphine Sulfate Extended-Release Tablets required and rely upon ad hoc* supplementation to deal with inadequate analgesia. (See discussion which follows.)

Use of Morphine Sulfate Extended-Release Tablets as the first opioid analgesic

There has been no systematic evaluation of Morphine Sulfate Extended-Release Tablets as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate a patient using extended-release morphine, it is ordinarily advisable to begin treatment using an immediate-release formulation.

Considerations in the Adjustment of Dosing Regimens

Whatever the approach, if signs of excessive opioid effects are observed early in a dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, "breakthrough" pain occurs late in the dosing interval, the dosing interval may be shortened. Alternatively, a supplemental dose of a short-acting analgesic may be given. As experience is gained, *adjustments can be made to obtain an appropriate balance between pain relief, opioid side effects,* and the convenience of the dosing schedule.

In adjusting dosing requirements, it is recommended that the dosing interval never be extended beyond 12 hours because the administration of very large single doses may lead to acute overdose. [Morphine Sulfate Extended-Release Tablets are an extended-release formulation; it does not release morphine continuously over the dosing interval.]

For patients with low daily morphine requirements, the 15 mg tablet should be used.

Special Instructions for Morphine Sulfate Extended-Release Tablets 200 mg Tablets (For use in opioid-tolerant patients only.)

The Morphine Sulfate Extended-Release Tablets 200 mg tablet is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. It is recommended that this strength be reserved for patients that have *already been titrated to a stable analgesic regimen using lower strengths of Morphine Sulfate Extended-Release Tablets* or other opioids.

Conversion from Morphine Sulfate Extended-Release Tablets to Parenteral Opioids

When converting a patient from Morphine Sulfate Extended-Release Tablets to parenteral opioids, it is best to assume that the parenteral to oral potency is high. NOTE THAT THIS IS THE CONVERSE OF THE STRATEGY USED WHEN THE DIRECTION OF CONVERSION IS FROM THE PARENTERAL TO ORAL FORMULATIONS. IN BOTH CASES, HOWEVER, THE AIM IS TO ESTIMATE THE NEW DOSE CONSERVATIVELY. For example, to estimate the required 24-hour dose of morphine for IM use, one could employ a conversion of 1 mg of morphine IM for every 6 mg of morphine as Morphine Sulfate Extended-Release Tablets. Of course, the IM 24-hour dose would have to be divided by six and administered on a q4h regimen. This approach is recommended because it is least likely to cause overdose.

SAFETY AND HANDLING

MORPHINE SULFATE EXTENDED-RELEASE TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED MORPHINE SULFATE EXTENDED-RELEASE TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

The morphine sulfate extended-release 200 mg tablet strength is for use in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. This strength is potentially toxic if accidentally ingested and patients and their families *should be instructed to take special care to avoid accidental or intentional ingestion by individuals other than those for whom the* medication was originally prescribed.

HOW SUPPLIED

Each Morphine Sulfate Extended-Release Tablet 15 mg is available as a round, blue convex tablet, one side debossed [M] and the other side debossed "15".

Bottles of 100 ..... NDC No. 0406-8315-01
Bottles of 500 ..... NDC No. 0406-8315-05
Unit Dose (10 x 10) ..... NDC No. 0406-8315-62
Punch Card (5 x 30) ..... NDC No. 0406-8315-32

Each Morphine Sulfate Extended-Release Tablet 30 mg is available as a round, purple convex tablet, one side debossed [M] and the other side debossed "30".

Bottles of 50 ..... NDC No. 0406-8330-50
Bottles of 100 ..... NDC No. 0406-8330-01
Bottles of 500 ..... NDC No. 0406-8330-05
Unit Dose (10 x 10) ..... NDC No. 0406-8330-62
Punch Card (5 x 30) ..... NDC No. 0406-8330-32

Each Morphine Sulfate Extended-Release Tablet 60 mg is available as a round, orange convex tablet, one side debossed [M] and the other side debossed "60".

Bottles of 100 ..... NDC No. 0406-8360-01
Bottles of 500 ..... NDC No. 0406-8360-05
Unit Dose (10 x 10) ..... NDC No. 0406-8360-62
Punch Card (5 x 30) ..... NDC No. 0406-8360-32

Each Morphine Sulfate Extended-Release Tablet 100 mg is available as a round, gray convex tablet, one side debossed [M] and the other side debossed "100".

Bottles of 100 ..... NDC No. 0406-8390-01
Bottles of 500 ..... NDC No. 0406-8390-05
Unit Dose (10 x 10) ..... NDC No. 0406-8390-62

Each Morphine Sulfate Extended-Release Tablet 200 mg is available as a capsule-shaped, green convex tablet, one side debossed [M] and the other side debossed "200".

Bottles of 100 ..... NDC No. 0406-8320-01

Storage: Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container.

CAUTION
DEA Order Form Required.

[M] is a registered trademark of Mallinckrodt Inc.

Mallinckrodt Inc.
675 McDonnell Blvd.
St. Louis, MO 63134

Printed in U.S.A.
MG #18897

tyco Healthcare

Mallinckrodt

Rev. 050204

85151203

OXYCODONE HYDROCHLORIDE TABLETS, USP 15 mg & 30 mg Rx only

OXYCODONE HYDROCHLORIDE
Tablets, USP
15 mg & 30 mg
Rx only

C II

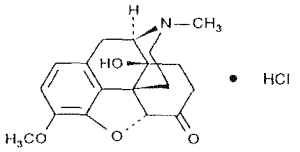
DESCRIPTION

Oxycodone Hydrochloride Tablets, USP are an opioid analgesic.

Each tablet for oral administration contains 15 mg or 30 mg of oxycodone hydrochloride USP.

Oxycodone hydrochloride is a white, odorless crystalline powder derived from the *opium* alkaloid, *thebaine*. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL) and is considered slightly soluble in alcohol (octanol water partition coefficient is 0.7).

Chemically, oxycodone hydrochloride is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride and has the following structural formula:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The tablets contain the following inactive ingredients: microcrystalline cellulose; sodium starch glycolate; corn starch; lactose monohydrate; stearic acid; D&C Yellow No. 10 (15 mg tablet); and FD&C Blue No. 2 (15 mg and 30 mg tablets).

The 15 mg and 30 mg tablets contain the equivalent of 13.5 mg and 27.0 mg, respectively, of oxycodone free base.

CLINICAL PHARMACOLOGY

Pharmacology:

The analgesic ingredient, oxycodone, is a semi-synthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these involves the central nervous system and organs composed of smooth muscle.

Oxycodone, as the hydrochloride salt, is a pure agonist opioid whose principal therapeutic action is analgesia and has been *in clinical use since 1917. Like all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial* agonists or non-opioid analgesics. Based upon a single-dose, relative-potency study conducted in humans with cancer pain, 10 to 15 mg of oxycodone given intramuscularly produced an analgesic effect similar to 10 mg of morphine given intramuscularly. Both drugs have a 3 to 4 hour duration of action. Oxycodone retains approximately one half of its analgesic activity when administered orally.

Effects on Central Nervous System: The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. A significant feature of opioid-induced analgesia is that it occurs without loss of consciousness. The relief of pain by morphine-like opioids is relatively selective, in that other sensory modalities, (e.g., touch, vibrations, vision, hearing, etc.) are not obtunded.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on Gastrointestinal Tract and Other Smooth Muscle: Oxycodone, like other opioid analgesics, produces some degree of nausea and vomiting which is caused by direct stimulation of the chemoreceptor trigger zone (CTZ) located in the medulla. The frequency and severity of emesis gradually diminishes with time.

Oxycodone may cause a decrease in the secretion of hydrochloric acid in the stomach reduces motility while increasing the *tone of the antrum, stomach, and duodenum. Digestion of food in the small intestine is* delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on Cardiovascular System: Oxycodone, in therapeutic doses, produces peripheral vasodilatation (arteriolar and venous), decreased peripheral resistance, and inhibits baroreceptor reflexes. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Caution should be used in hypovolemic patients, such as those suffering acute myocardial infarction, because oxycodone may cause or further aggravate their hypotension. Caution should also be used in patients with cor pulmonale who have received therapeutic doses of opioids.

Pharmacodynamics:

The relationship between the plasma level of oxycodone and the analgesic response will depend on the patient's age, state of health, medical condition and extent of previous opioid treatment.

The minimum effective plasma concentration of oxycodone to achieve analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. Thus, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or development of tolerance.

Pharmacokinetics:

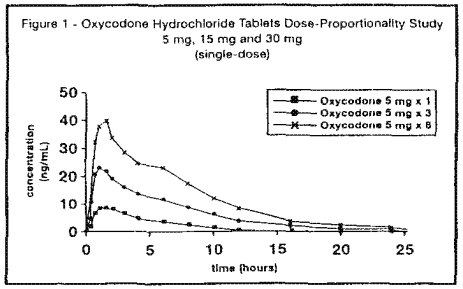
The activity of Oxycodone Hydrochloride Tablets is primarily due to the parent drug oxycodone. Oxycodone Hydrochloride Tablets are designed to provide immediate release of oxycodone.

Table 1
Pharmacokinetic Parameters (Mean±SD)

Dose\Parameters	AUC (ngxhr/mL)	Cmax (ng/mL)	Tmax (hr)	Cmin (ng/mL)	Cavg (ng/mL)	Half-Life (hr)
Single Dose Pharmacokinetics						
Oxycodone Hydrochloride Tablets 5 mg tabs x 3	133.2±33	22.3±8.2	1.8±1.8	n/a	n/a	3.73±0.9
Oxycodone Hydrochloride Tablets 15 mg tab	128.2±35.1	22.2±7.6	1.4±0.7	n/a	n/a	3.55±1.0
Oxycodone Hydrochloride Oral Concentrate Solution 15 mg oral solution	130.6±34.7	21.1±6.1	1.9±1.5	n/a	n/a	3.7±0.8
Oxycodone Hydrochloride Tablets 30 mg tab	268.2±60.7	39.3±14.0	2.6±3.0	n/a	n/a	3.85±1.3
Food-Effect, Single Dose						
Oxycodone Hydrochlonde Oral Solution, USP 10 mg/10 mL oral sol'n (fasted)	105±6.2	19.0±3.7	1.25±0.5	n/a	n/a	2.9±0.4
Oxycodone Hydrochloride Oral Solution, USP 10mg/10 mL oral sol'n (fed)	133±25.2	17.7±3.0	2.54±1.2	n/a	n/a	3.3±0.5
Multiple-Dose Studies	AUC(72-84)					
Oxycodone Hydrochloride Tablets 5 mg tabs q6h x 14 doses	113.3±24.0	15.7±3.2	1.3±0.3	7.4±1.8	9.4±2.0	n/a
Oxycodone Hydrochloride Oral Solution, USP 3.33 mg (3.33 mL) oral sol'n. q4h x 21 doses	99.0±24.8	12.9±3.1	1.0±0.3	7.2±2.3	9.7±2.6	n/a

Absorption: About 60% to 87% of an oral dose of oxycodone reaches the systemic circulation in comparison to a parenteral dose. This high oral bioavailability (compared to other oral opioids) is due to lower pre-systemic and/or first-pass metabolism of oxycodone. The relative oral bioavailability of Oxycodone Hydrochloride Tablets 15 mg and 30 mg tablets, compared to the 5 mg Oxycodone Hydrochloride Tablets, is 96% and 101% respectively. Oxycodone Hydrochloride Tablets 15 mg tablets and 30 mg tablets are bioequivalent to the 5 mg Oxycodone Hydrochloride Tablets (see Table 1 for pharmacokinetic parameters). Dose proportionality of oxycodone has been established using the Oxycodone Hydrochloride Tablets 5mg tablets at doses of 5 mg, 15 mg (three 5 mg tablets) and 30 mg (six 5 mg tablets) based on extent of absorption (AUC) (see Figure 1). It takes approximately 18 to 24 hours to reach steady-state plasma concentrations of oxycodone with Oxycodone Hydrochloride Tablets.

Figure 1 - Oxycodone Hydrochloride Tablets Dose-Proportionality Study
5 mg, 15 mg and 30 mg
(single-dose)



Food Effect: A single-dose food effect study was conducted in normal volunteers using the 5 mg/5 mL solution. The concurrent intake of a high fat meal was shown to enhance *the extent (27% increase in AUC), but not the rate of oxycodone* absorption from the oral solution, (see Table 1). In addition, food caused a delay in Tmax (1.25 to 2.54 hour). Similar effects of food are expected with the 15 mg and 30 mg tablets.

Distribution: Following intravenous administration, the volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Plasma protein binding of oxycodone at 37°C and a pH of 7.4 was about 45%. Oxycodone has been found in breast milk. (see PRECAUTIONS-Nursing Mothers.)

Metabolism: Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Oxymorphone is present in the plasma only in low concentrations. The analgesic activity profile of other metabolites is not known at present.

The formation of oxymorphone, but not noroxycodone, is mediated by CYP2D6 and as such its formation can, in theory, be affected by other drugs. (see PRECAUTIONS-Drug Interactions.)

Elimination: Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults. Apparent elimination half-life of oxycodone following the administration of Oxycodone Hydrochloride Tablets was 3.5 to 4 hours.

Special Populations:

Geriatric: Population pharmacokinetic studies conducted with Oxycodone Hydrochloride Tablets, indicated that the plasma concentrations of oxycodone did not appear to be increased *in patients over the age of 65.*

Gender: Population pharmacokinetic analyses performed in the clinical study support the lack of gender effect on the pharmacokinetics of oxycodone from Oxycodone Hydrochloride Tablets.

Race: Population pharmacokinetic analyses support the lack of race effect on oxycodone pharmacokinetics after administration of Oxycodone Hydrochloride Tablets, but these data should be interpreted conservatively, since the majority of patients enrolled into the studies were Caucasians (94%).

Renal Insufficiency: In a clinical trial supporting the development of Oxycodone Hydrochloride Tablets, too few patients with decreased renal function were evaluated to study these potential differences. In previous studies, patients with renal impairment (defined as a creatinine clearance < 60 mL/min) had concentrations of oxycodone in the plasma that were higher than in subjects with normal renal function. Based on information available on the metabolism and excretion of oxycodone, dose initiation in patients with renal impairment should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Hepatic Failure: In a clinical trial supporting the development of Oxycodone Hydrochloride Tablets, too few patients with decreased hepatic function were evaluated to study these potential differences. However, since oxycodone is extensively metabolized, its clearance may decrease in hepatic failure patients. Dose initiation *in patients with hepatic impairment should* follow a conservative approach. Dosages should be adjusted according to the clinical situation.

INDICATIONS AND USAGE

Oxycodone Hydrochloride Tablets are an immediate-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where the use of an opioid analgesic is appropriate.

CONTRAINDICATIONS

Oxycodone Hydrochloride Tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment) and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone Hydrochloride Tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

Respiratory Depression:

Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone Hydrochloride Tablets should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of Oxycodone Hydrochloride Tablets may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Hypotensive Effect:

Oxycodone Hydrochloride Tablets, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone Hydrochloride Tablets may produce orthostatic hypotension in ambulatory patients. Oxycodone Hydrochloride Tablets, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilatation produced by the drug may further reduce cardiac output and blood pressure.

Head Injury and Increased Intracranial Pressure:

The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

PRECAUTIONS

General:

Oxycodone Hydrochloride Tablets are intended for use in patients who require oral pain therapy with an opioid agonist. As with any opioid analgesic, it is critical to adjust the dosing regimen individually for each patient (see DOSAGE AND ADMINISTRATION).

Selection of patients for treatment with Oxycodone Hydrochloride Tablets should be governed by the same principles that apply to the use of other potent opioid analgesics. Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension. Physicians should individualize treatment in every case, using nonopioid analgesics, prn opioids and /or combination products, and chronic opioid therapy with drugs such as Oxycodone Hydrochloride Tablets in a progressive plan of pain management such as outlined by the World Health Organization, the Agency for Health Care Policy and Research, and *the American Pain Society.*

Use of Oxycodone Hydrochloride Tablets is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's *disease); convulsive disorders; CNS* depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of Oxycodone Hydrochloride Tablets, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Tolerance and Physical Dependence:

Physical dependence and tolerance are not unusual during chronic opioid therapy. Significant tolerance should not occur in *most patients treated with the lowest doses of oxycodone. It should be expected, however, that a fraction of patients will* develop some degree of tolerance and require progressively higher dosages of Oxycodone Hydrochloride Tablets to maintain pain control during chronic treatment. The dosage should be selected according to the patient's individual analgesic response and ability to tolerate side effects. Tolerance to the analgesic effects of opioids is usually paralleled by tolerance to side effects except for constipation.

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OXYCODONE HYDROCHLORIDE TABLETS, USP
15 mg & 30 mg
Rx only

Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with opioid antagonist activity. If Oxycodone Hydrochloride Tablets are abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur (see **DRUG ABUSE AND DEPENDENCE**). If signs and symptoms of withdrawal occur, patients should be treated by reinstitution of opioid therapy followed by gradual tapered dose reduction of Oxycodone Hydrochloride Tablets combined with symptomatic support (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Use In Pancreatic/Biliary Tract Disease:

Oxycodone Hydrochloride Tablets may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like Oxycodone Hydrochloride Tablets may cause increases in the serum amylase level.

Information for Patients/Caregivers:

If clinically advisable, patients (or their caregivers) receiving Oxycodone Hydrochloride Tablets should be given the following information by the physician, nurse, pharmacist or caregiver:

1. Patients should be advised to report episodes of break through pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
2. Patients should be advised not to adjust the dose of Oxycodone Hydrochloride Tablets without consulting the prescribing professional.
3. Patients should be advised that Oxycodone Hydrochloride Tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
4. Patients should not combine Oxycodone Hydrochloride Tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
5. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
6. Patients should be advised that Oxycodone Hydrochloride Tablets are a potential drug of abuse. They should protect them from theft, and they should never be given to anyone other than the individual for whom they were prescribed.
7. Patients should be advised that if they have been receiving treatment with Oxycodone Hydrochloride Tablets for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the Oxycodone Hydrochloride Tablets dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Drug Interactions:

Oxycodone is metabolized in part to oxymorphone via the cytochrome p450 isoenzyme CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. However, clinicians should be aware of this possible interaction.

Neuromuscular Blocking Agents: Oxycodone, as well as other opioid analgesics, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

CNS Depressants: Patients receiving narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with Oxycodone Hydrochloride Tablets may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual dosage of Oxycodone Hydrochloride Tablets. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol and buprenorphine) should be administered with caution to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as Oxycodone Hydrochloride Tablets. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of Oxycodone Hydrochloride Tablets and/or may precipitate withdrawal symptoms in these patients.

Monoamine Oxidase Inhibitors (MAOIs): MAOIs have been reported to intensify the effects of at least one opioid drug causing anxiety, confusion and significant depression of respiration or coma. The use of Oxycodone Hydrochloride Tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term studies have not been performed in animals to evaluate the carcinogenic potential of Oxycodone Hydrochloride Tablets or oxycodone. The possible effects on male or female fertility have not been studied in animals.

Pregnancy:

Teratogenic Effects: Category B: Reproduction studies in Sprague-Dawley rats and New Zealand rabbits revealed that when oxycodone was administered orally at doses up to 16 mg/kg (approximately 2 times the daily oral dose of 90 mg for adults on a mg/m^2 basis) and 25 mg/kg (approximately 5 times the daily oral dose of 90 mg on a mg/m^2 basis), respectively was not teratogenic or embryo-fetal toxic. There are no adequate and well controlled studies of oxycodone in pregnant women. Because animal reproductive studies are not always predictive of human responses, Oxycodone Hydrochloride Tablets should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Neonates whose mothers have taken oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery:

Oxycodone Hydrochloride Tablets are not recommended for use in women during or immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. Neonates, whose mothers received opioid analgesics during labor, should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

Nursing Mothers:

Oxycodone has been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving Oxycodone Hydrochloride Tablets since oxycodone may be excreted in milk.

Pediatric Use:

The safety and efficacy of oxycodone immediate release in pediatric patients have not been evaluated.

Geriatric Use:

Of the total number of subjects in clinical studies of Oxycodone Hydrochloride Tablets, 20.8% (112/538) were 65 and over, while 7.2% (39/538) were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment:

Since oxycodone is extensively metabolized, its clearance may decrease in hepatic failure patients. Dose initiation in patients with hepatic impairment should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Renal Impairment:

Published data reported that elimination of oxycodone was impaired in end-stage renal failure. Mean elimination half-life was prolonged in uremic patients due to increased volume of distribution and reduced clearance. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Ambulatory Patients:

Oxycodone Hydrochloride Tablets may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

ADVERSE REACTIONS

Oxycodone Hydrochloride Tablets have been evaluated in open label clinical trials in patients with cancer and nonmalignant pain. Oxycodone Hydrochloride Tablets are associated with adverse experiences similar to those seen with other opioids.

Serious adverse reactions that may be associated with Oxycodone Hydrochloride Tablets therapy in clinical use are those observed with other opioid analgesics and include: respiratory depression, respiratory arrest, circulatory depression, cardiac arrest, hypotension, and/or shock (see **OVERDOSE, WARNINGS**).

The less severe adverse events seen on initiation of therapy with Oxycodone Hydrochloride Tablets are also typical opioid side effects. These events are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent of these include nausea, constipation, vomiting, headache, and pruritus.

In many cases the frequency of adverse events during initiation of opioid therapy may be minimized by careful individualization of starting dosage, slow titration and the avoidance of large rapid swings in plasma concentration of the opioid. Many of these adverse events will abate as therapy is continued and some degree of tolerance is developed, but others may be expected to remain throughout therapy.

In all patients for whom dosing information was available (n=191) from the open-label and double-blind studies involving Oxycodone Hydrochloride Tablets, the following adverse events were recorded in patients treated with Oxycodone Hydrochloride Tablets with an incidence ≥ 3%. In descending order of frequency they were: nausea, constipation, vomiting, headache, pruritus, insomnia, dizziness, asthenia, and somnolence.

The following adverse experiences occurred in less than 3% of patients involved in clinical trials with oxycodone:

Body as a Whole: abdominal pain, accidental injury, allergic reaction, back pain, chills and fever, fever, flu syndrome, infection, neck pain, pain, photosensitivity reaction, and sepsis.
Cardiovascular: deep thrombophlebitis, heart failure, hemorrhage, hypotension, migraine, palpitation, and tachycardia.
Digestive: anorexia, diarrhea, dyspepsia, dysphagia, gingivitis, glossitis, and nausea and vomiting.
Hemic and Lymphatic: anemia and leukopenia.
Metabolic and Nutritional: edema, gout, hyperglycemia, iron deficiency anemia and peripheral edema.
Musculoskeletal: arthralgia, arthritis, bone pain, myalgia and pathological fracture.
Nervous: agitation, anxiety, confusion, dry mouth, hypertonia, hypesthesia, nervousness, neuralgia, personality disorder, tremor, and vasodilation.
Respiratory: bronchitis, cough increased, dyspnea, epistaxis, laryngismus, lung disorder, pharyngitis, rhinitis, and sinusitis.
Skin and Appendages: herpes simplex, rash, sweating, and urticaria.
Special Senses: amblyopia.
Urogenital: urinary tract infection.

DRUG ABUSE AND DEPENDENCE

Controlled Substance:

Oxycodone Hydrochloride Tablets are a Schedule II narcotic under the U.S. Controlled Substances Act (CSA) (21 U.S.C. 801-886). Oxycodone Hydrochloride Tablets can produce drug dependence of the morphine type, and therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration. Oxycodone Hydrochloride Tablets should be prescribed and administered with the same degree of caution appropriate to the use of other narcotic-containing medications.

Abuse:

Since Oxycodone Hydrochloride Tablets are a mu-opioid agonist, it may be subject to misuse, abuse, and addiction. Addiction to opioids prescribed for pain management has not been estimated. However, requests for opioids from opioid-addicted patients occur. As such, physicians should take appropriate care in prescribing Oxycodone Hydrochloride Tablets.

Dependence:

Opioid analgesics may cause psychological and physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug after long term administration. Also, symptoms of withdrawal may be precipitated through the administration of drugs with muopioid antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine, dezocine). (see also OVERDOSAGE section). Physical dependence usually does not occur to a clinically significant degree, until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required to produce the same degree of analgesia, is initially manifested by a shortened duration of an analgesic effect and subsequently, by decreases in the intensity of analgesia.

In chronic pain patients, and in opioid-tolerant cancer patients, the administration of Oxycodone Hydrochloride Tablets should be guided by the degree of tolerance manifested and the doses needed to adequately relieve pain.

The severity of the Oxycodone Hydrochloride Tablets abstinence syndrome may depend on the degree of physical dependence. Withdrawal is characterized by rhinitis, myalgia, abdominal cramping, and occasional diarrhea. Most observable symptoms disappear in 5 to 14 days without treatment; however, there may be a phase of secondary or chronic abstinence which may last for 2 to 6 months characterized by insomnia, irritability, and muscular aches. The patient may be detoxified by gradual reduction of the dose. Gastrointestinal disturbances or dehydration should be treated with supportive care.

OVERDOSAGE

Signs and Symptoms:

Acute overdose with Oxycodone Hydrochloride Tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Treatment:

To treat Oxycodone Hydrochloride Tablets overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The narcotic antagonists, naloxone or nalmefene, are specific antidotes for opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to Oxycodone Hydrochloride Tablets overdose. If needed the appropriate dose of naloxone hydrochloride or nalmefene should be administered simultaneously with efforts at respiratory resuscitation (see package insert for each drug for the details). Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. Gastric emptying may be useful in removing unabsorbed drug.

Opioid antagonists should be administered cautiously to persons who are suspected to be physically dependent on any opioid agonist, including oxycodone. (see **Opioid-Tolerant Individuals**).

Opioid-Tolerant Individuals: In an individual physically dependent on opioids, administration of a usual dose of antagonist will precipitate an acute withdrawal. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of an opioid antagonist should be reserved for cases where such treatment is clearly needed. If it is necessary to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses.

DOSAGE AND ADMINISTRATION

Oxycodone Hydrochloride Tablets are intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic. The dose should be individually adjusted according to severity of pain, patient response and patient size. If the pain increases in severity, if analgesia is not adequate, or if tolerance occurs, a gradual increase in dosage may be required.

Patients who have not been receiving opioid analgesics should be started on Oxycodone Hydrochloride Tablets in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain. The dose should be titrated based upon the individual patient's response to their initial dose of Oxycodone Hydrochloride Tablets. Patients with chronic pain should have their dosage given on an around-the-clock basis to prevent the reoccurrence of pain rather than treating the pain after it has occurred. This dose can then be adjusted to an acceptable level of analgesia taking into account side effects experienced by the patient.

For control of severe chronic pain, Oxycodone Hydrochloride Tablets should be administered on a regularly scheduled basis, every 4 to 6 hours, at the lowest dosage level that will achieve adequate analgesia.

As with any potent opioid, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is not possible to list every condition that is important to the selection of the initial dose of Oxycodone Hydrochloride Tablets, attention should be given to: 1) the daily dose, potency, and characteristics of a pure agonist or mixed agonist/antagonist the patient has been taking previously, 2) the reliability of the relative potency estimate to calculate the dose of oxycodone needed, 3) the degree of opioid tolerance, 4) the general condition and medical status of the patient, and 5) the balance between pain control and adverse experiences.

Conversion From Fixed-Ratio Opioid/Acetaminophen, Opioid/Aspirin, or Opioid / Nonsteroidal Combination Drugs:

When converting patients from fixed ratio opioid/non-opioid drug regimens a decision should be made whether or not to continue the non-opioid analgesic. If a decision is made to discontinue the use of non-opioid analgesic, it may be necessary to titrate the dose of Oxycodone Hydrochloride Tablets in response to the level of analgesia and adverse effects afforded by the dosing regimen. If the non-opioid regimen is continued as a separate single entity agent, the starting dose Oxycodone Hydrochloride Tablets should be based upon the most recent dose of opioid as a baseline for further titration of oxycodone. Incremental increases should be gauged according to side effects to an acceptable level of analgesia.

Patients Currently on Opioid Therapy:

If a patient has been receiving opioid-containing medications prior to taking Oxycodone Hydrochloride Tablets, the potency of the prior opioid relative to oxycodone should be factored into the selection of the total daily dose (TDD) of oxycodone.

In converting patients from other opioids to Oxycodone Hydrochloride Tablets close observation and adjustment of dosage based upon the patient's response to Oxycodone Hydrochloride Tablets is imperative. Administration of supplemental analgesia for breakthrough or incident pain and titration of the total daily dose of Oxycodone Hydrochloride Tablets may be necessary, especially in patients who have disease states that are changing rapidly.

Maintenance of Therapy:

Continual re-evaluation of the patient receiving Oxycodone Hydrochloride Tablets is important, with special attention to the maintenance of pain control and the relative incidence of side effects associated with therapy. If the level of pain increases, effort should be made to identify the source of increased pain, while adjusting the dose as described above to decrease the level of pain.

During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), the continued need for the use of opioid analgesics should be reassessed as appropriate.

Cessation of Therapy:

When a patient no longer requires therapy with Oxycodone Hydrochloride Tablets or other opioid analgesics for the treatment of their pain, it is important that therapy be gradually discontinued over time to prevent the development of an opioid abstinence syndrome (narcotic withdrawal). In general, therapy can be decreased by 25% to 50% per day with careful monitoring for signs and symptoms of withdrawal (see **Drug Abuse and Dependence** section for description of the signs and symptoms of withdrawal). If the patient develops these signs or symptoms, the dose should be raised to the previous level and titrated down more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. It is not known at what dose of Oxycodone Hydrochloride Tablets that treatment may be discontinued without risk of the opioid abstinence syndrome.

HOW SUPPLIED

Each Oxycodone Hydrochloride Tablet, USP 15 mg is available as a light green round convex tablet with a Ⓜ on one side and "15" above a bisect on the other.

Bottles of 100 ..... NDC 0406-8515-01

Each Oxycodone Hydrochloride Tablet, USP 30 mg is available as a light blue round convex tablet with a Ⓜ on one side and "30" above a bisect on the other.

Bottles of 100 ..... NDC 0406-8530-01

DEA Order Form Required

Dispense in tight, light-resistant container with child-resistant closure.

Protect from moisture.

Store at 25°C (77°F) Controlled Room Temperature with brief excursions permitted between 15° to 30°C (59° to 86°F) [see USP].

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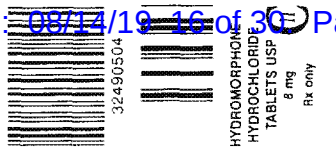
Mallinckrodt Inc.
St. Louis, MO 63134 U.S.A.
MG #19018

Mallinckrodt

Rev. 122603



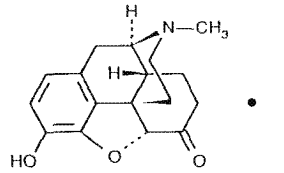
HYDROMORPHONE HYDROCHLORIDE TABLETS USP
8 mg
Rx only

C II

DESCRIPTION

Hydromorphone hydrochloride tablets USP, 8 mg are supplied in tablet form for oral administration.

Hydromorphone hydrochloride, a hydrogenated ketone of morphine, is a narcotic analgesic. The structural formula of hydromorphone hydrochloride is:



$C_{17}H_{19}NO_3 \cdot HCl$ MW = 321.80

Each hydromorphone hydrochloride tablet USP, 8 mg contains:
Hydromorphone Hydrochloride, USP . . . . . 8 mg

In addition, each tablet contains the following inactive ingredients: lactose monohydrate NF, *magnesium stearate NF, microcrystalline cellulose NF and stearic acid NF.*

CLINICAL PHARMACOLOGY

Many of the effects described below are common to this class of mu-opioid agonist analgesics. *In some instances, data may not exist to distinguish the effects of hydromorphone* hydrochloride tablets from those observed with other opioid analgesics. However, in the absence of data to the contrary, it is assumed that hydromorphone hydrochloride tablets would possess all the actions of mu-agonist opioids.

Opioid analgesics exert their primary effects on the central nervous system and organs containing smooth muscle. The principal actions of therapeutic value are analgesia and sedation. A significant feature of the analgesia is that it can occur without loss of consciousness. Opioid analgesics also suppress the cough reflex and may cause respiratory depression, mood changes, mental clouding, euphoria, dysphoria, nausea, and vomiting and electroencephalographic changes.

The precise mode of analgesic action of opioid analgesics is unknown. However, specific CNS opiate receptors have been identified. Opioids are believed to express their pharmacological effects by combining with these receptors.

Opioids depress the cough reflex by direct effect on the cough center in the medulla.

Opioids depress the respiratory reflex by a direct effect on brain stem respiratory centers. The mechanism of respiratory depression also involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension.

Opioids cause miosis. Pinpoint pupils are a common sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings) and marked mydriasis occurs with asphyxia.

Gastric, biliary and pancreatic secretions are decreased by opioids. Opioids cause a reduction in motility associated with an increase in tone in the gastric antrum and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, and tone may be increased to the point of spasm. The end result is constipation. Opioids can cause a marked increase in biliary tract *pressure as a result of spasm* of the sphincter of Oddi.

Certain opioids produce peripheral vasodilation which may result in orthostatic hypotension. Release of histamine may occur with opioids and may contribute to drug-induced hypotension. Other manifestations of histamine release may include pruritus, flushing, and red eyes.

The dosage of opioid analgesics like hydromorphone should be individualized for any given patient, since adverse events can occur at doses that may not provide complete freedom from pain. (*see* INDIVIDUALIZATION OF DOSAGE).

Pharmacokinetics

The analgesic activity of hydromorphone hydrochloride is due to the parent drug, hydromorphone. Hydromorphone is rapidly absorbed from the gastrointestinal tract after oral administration and undergoes extensive first-pass metabolism. *In vivo* bioavailability following single-dose administration of the hydromorphone hydrochloride tablet, 8 mg is approximately 24% (coefficient of variation 21%). Dose proportionality between hydromorphone hydrochloride tablets 8 mg and other strengths of hydromorphone hydrochloride tablets (2 mg and 4 mg) has *not been established.*

Absorption

After oral administration of hydromorphone hydrochloride tablets, 8 mg, peak plasma hydromorphone concentrations are generally attained within $^1/_2$ to 1-hour.

	Mean (%cv)			
Dosage Form	C_{max} (mg)	T_{max} (hrs)	AUC (mg*hr/mL)	$T_{1/2}$ (hrs)
8 mg Tablet	5.5 (33%)	0.74 (34%)	23.7 (28%)	2.6 (18%)

Food effects: The effect on the rate and extent of absorption of hydromorphone hydrochloride tablets when given with food has not been studied.

Distribution

At therapeutic plasma levels, hydromorphone is approximately 8 to 19% bound to plasma proteins. After an i.v. bolus dose, the steady state of volume distribution [mean (%cv)] is 302.9(32%) liters.

Metabolism

Hydromorphone is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites.

Elimination

Only a small amount of the hydromorphone dose is excreted unchanged in the urine. Most of the dose is excreted as hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites. The systemic clearance is approximately 1.96 (20%) liters/minute. The terminal elimination half-life of hydromorphone after an i.v. dose is about 2.3 hours.

Special Populations

Pediatrics: Pharmacokinetics of hydromorphone have not been evaluated in children.

Hepatic and renal impairment: The effects of hepatic and renal disease on the clearance of hydromorphone are unknown but caution should be taken to guard against possible accumulation if hepatic and/or renal functions are seriously impaired.

Pregnancy and nursing mothers: Hydromorphone crosses the placenta. Hydromorphone is also found in low levels in breast milk, and may causerespiratory compromise in newborns when administered during labor or delivery.

CLINICAL TRIALS

Analgesic effects of single doses of hydromorphone hydrochloride oral liquid administered to patients with post-surgical pain have been studied in double-blind controlled trials. In one study with 61 patients, both 5 mg and 10 mg of hydromorphone hydrochloride oral liquid provided significantly more analgesia than placebo. In another trial with 80 patients, 5 mg and 10 mg of hydromorphone hydrochloride oral liquid were compared to 30 mg and 60 mg of morphine sulfate oral liquid. The pain relief provided by 5 mg and 10 mg hydromorphone hydrochloride oral liquid was comparable to 30 mg and 60 mg oral morphine sulfate, respectively.

INDIVIDUALIZATION OF DOSAGE

Safe and effective administration of opioid analgesics to patients with acute or chronic pain depends upon a comprehensive assessment of the patient. The nature of the pain (severity, frequency, etiology, and pathophysiology) as well as the concurrent medical status of the patient will affect selection of the starting dosage.

In non-opioid-tolerant patients, therapy with hydromorphone is typically initiated at an oral dose of 2 to 4 mg every four hours, but elderly patients may require lower doses (*see* ***PRECAUTIONS*** *-Geriatric Use).*

In patients receiving opioids, both the dose and duration of analgesia will vary substantially depending on the patient's opioid tolerance. The dose should be selected and adjusted so that *at least 3 to 4 hours of pain relief may be achieved. In patients taking opioid analgesics, the* starting dose of hydromorphone hydrochloride should be based on prior opioid usage. This should be done by converting the total daily usage of the previous opioidto an equivalent total daily dosage of *oral hydromorphone hydrochloride* using an equianalgesic table (see below). For opioids not in the table, first estimate the equivalent total daily usage of oral morphine, then use the table to find the equivalent total daily dosage of hydromorphone hydrochloride.

Once the total daily dosage of hydromorphone hydrochloride has been estimated, it should be divided into the desired number of doses. Since there is individual variation in response to different opioid drugs, only $^1/_2$ to $^2/_3$ of the estimated dose of hydromorphone hydrochloride calculated from equivalence tables should be given for the first few doses, then increased as needed according to the patient's response.

In chronic pain, doses should be administered around-the-clock. A supplemental dose of 5 to 15% of the total daily usage may be administered every two hours on an "as-needed" basis.

Periodic reassessment after the initial dosing is always required. If pain management is not satisfactory and in the absence of significant opioid-induced adverse events, the hydromorphone dose may be increased gradually. If excessive opioid side effects are observed early *in the dosing interval, the hydromorphone dose should be reduced. If this results in* breakthrough pain at the end of the dosing interval, the dosing interval may need to be shortened. Dose titration should be guided more by the need for analgesia than the absolute dose of opioid employed.

OPIOID ANALGESIC EQUIVALENTS WITH APPROXIMATELY EQUIANALGESIC POTENCY*

Nonproprietary (Trade) Name	IM or SC Dose	ORAL Dose
Morphine sulfate	10 mg	40 to 60 mg
Hydromorphone HCl (DILAUDID)	*1.3 to 2 mg*	6.50 to 7.5 mg
Oxymorphone HCl (Numorphan)	1 to 1.1 mg	6.6 mg
Levorphanol tartrate (Levo-Dromoran)	2 to 2.3 mg	4 mg
Meperidine, pethidine HCl (Demerol)	75 to 100 mg	300 to 400 mg
Methadone HCl (Dolophine)	10 mg	10 to 20 mg

*Dosages and ranges of dosages represented, are a compilation of estimated equipotent dosages from published references comparing opioid analgesics in cancer and severe pain.

INDICATIONS AND USAGE

Hydromorphone hydrochloride tablets are indicated for the management of pain in patients where an opioid analgesic is appropriate.

CONTRAINDICATIONS

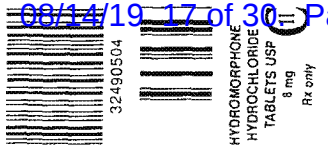
Hydromorphone hydrochloride tablets are contraindicated in: patients with known hypersensitivity to hydromorphone, patients with respiratory depression in the absence of resuscitative equipment, and in patients with status asthmaticus. Hydromorphone hydrochloride tablets are also contraindicated for use in obstetrical analgesia.

WARNINGS

Impaired Respiration: Respiratory depression is the chief hazard of hydromorphone hydrochloride tablets. Respiratory depression occurs most frequently in overdose situations, in the elderly, in the debilitated, and in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Hydromorphone hydrochloride tablets should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially *decreased respiratory reserve, hypoxia, hypercapnia,* or in patients with preexisting respiratory depression. In such patients even usual therapeutic doses of opioid analgesics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Drug Dependence: Hydromorphone hydrochloride *is a Schedule II narcotic. Hydromorphone* hydrochloride tablets can produce drug dependence of the morphine type and therefore have the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of hydromorphone hydrochloride, which should be prescribed and administered with the degree of caution appropriate to the use of morphine. Abrupt discontinuance in the administration of hydromorphone hydrochloride tablets in patients who are physically dependent on opioids is likely to result in a withdrawal syndrome (*see* **DRUG ABUSE AND DEPENDENCE**).



PRECAUTIONS

Special Risk Patients: In general, opioids should be given with caution and the initial dose should be reduced in the elderly or debilitated and those with severe impairment of hepatic, pulmonary or renal functions; myxedema or hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; gall bladder disease; acute alcoholism; delirium tremens; kyphoscoliosis or following gastrointestinal surgery.

The administration of opioid analgesics including hydromorphone hydrochloride tablets may obscure the diagnoses or clinical course in patients with acute abdominal conditions and may aggravate preexisting convulsions in patients with convulsive disorders.

Reports of mild to severe seizures and myoclonus have been reported in severely compromised patients, administered high doses of parenteral hydromorphone, for cancer and severe pain. Opioid administration at very high doses is associated with seizures and myoclonus in a variety of diseases where pain control is the primary focus.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of hydromorphone hydrochloride tablets with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or preexisting increase in intracranial pressure. Opioid analgesics including hydromorphone hydrochloride tablets may produce effects which can obscure the clinical course and neurologic signs of further increase in intracranial pressure in patients with head injuries.

Hypotensive Effect: Opioid analgesics, including hydromorphone hydrochloride tablets, may cause severe hypotension in an individual whose ability to maintain blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics (*see also* **PRECAUTIONS** -*Drug Interactions*). Therefore, hydromorphone hydrochloride tablets should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Use in Ambulatory Patients: Hydromorphone hydrochloride tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients should be cautioned accordingly. Hydromorphone hydrochloride may produce orthostatic hypotension in ambulatory patients. The addition of other CNS depressants to hydromorphone hydrochloride therapy may produce additive depressant effects, and hydromorphone hydrochloride should not be taken with alcohol.

Use in Biliary Surgery: Opioid analgesics including hydromorphone hydrochloride tablets should also be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi.

Use in Drug and Alcohol Dependent Patients: Hydromorphone hydrochloride should be used with caution in patients with alcoholism and other drug dependencies due to the increased frequency of narcotic tolerance, dependence, and the risk of addiction observed in these patient populations. Abuse of hydromorphone hydrochloride in combination with other CNS depressant drugs can result in serious risk to the patient.

Drug Interactions: The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including hydromorphone hydrochloride tablets, may enhance the action of neuromuscular blocking agents and produce an excessive degree of respiratory depression.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals to evaluate the drug's carcinogenic and mutagenic potential or the affect on fertility, have not been conducted.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Literature reports of hydromorphone hydrochloride administration to pregnant Syrian hamsters show that hydromorphone hydrochloride is teratogenic at a dose of 20 mg/kg which is 600 times the human dose. A maximal teratogenic effect (50% of fetuses affected) in the Syrian hamster was observed at a dose of 125 mg/kg (738 mg/m^2). There are no well-controlled studies in women. Hydromorphone is known to cross placental membranes. Hydromorphone hydrochloride tablets should be used in pregnant women only if the potential benefit justifies the potential risk to the fetus (*see Labor and Delivery* and **DRUG ABUSE AND DEPENDENCE**).

Labor and Delivery: Hydromorphone hydrochloride tablets are contraindicated in Labor and Delivery (*see* **CONTRAINDICATIONS**).

Nursing Mothers: Low levels of opioid analgesics have been detected in human milk. As a general rule, nursing should not be undertaken while a patient is receiving hydromorphone hydrochloride tablets since it, and other drugs in this class, may be excreted in the milk.

Pediatric Use: Safety and effectiveness in children have not been established.

Geriatric Use: Clinical studies of hydromorphone hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (*see* **INDIVIDUALIZATION OF DOSAGE** and **PRECAUTIONS**).

ADVERSE REACTIONS

The adverse effects of hydromorphone hydrochloride tablets are similar to those of other agonist opioid analgesics, and represent established pharmacological effects of the drug class. The major hazards include respiratory depression and apnea. To a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest have occurred.

The most frequently observed adverse effects are light-headedness, dizziness, sedation, nausea, vomiting, sweating, flushing, dysphoria, euphoria, dry mouth, and pruritus. These effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Syncopal reactions and related symptoms in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed with Opioid Analgesics: General and CNS: Weakness, headache, agitation, tremor, uncoordinated muscle movements, alterations of mood (nervousness, apprehension, depression, floating feelings, dreams), muscle rigidity, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis, transient hallucinations and disorientation, visual disturbances, insomnia and increased intracranial pressure may occur.

Cardiovascular: Chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension have been reported.

Respiratory: Bronchospasm and laryngospasm have been known to occur.

Gastrointestinal: Constipation, biliary tract spasm, ileus, anorexia, diarrhea, cramps and taste alteration have been reported.

Genitourinary: Urinary retention or hesitancy, and antidiuretic effects have been reported.

Dermatologic: Urticaria, other skin rashes, and diaphoresis.

DRUG ABUSE AND DEPENDENCE

Hydromorphone hydrochloride is a Schedule II narcotic, similar to morphine. Opioid analgesics may cause psychological and physical dependence (*see* **WARNINGS**). Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal symptoms also may be precipitated in the patient with physical dependence by the administration of a drug with opioid antagonist activity, e.g., naloxone (*see also* **OVERDOSAGE**).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage, but it may become clinically detectable after as little as a week. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia. In chronic pain patients, and in opioid-tolerant cancer patients, the dose of hydromorphone hydrochloride tablets should be guided by the degree of tolerance manifested.

In chronic pain patients in whom opioid analgesics including hydromorphone hydrochloride tablets are abruptly discontinued, a severe abstinence syndrome should be anticipated. This may be similar to the abstinence syndrome noted in patients who withdraw from heroin. Because of excessive loss of fluids through sweating, or vomiting and diarrhea, patients experiencing the syndrome usually exhibit marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse can occur. Without treatment most observable symptoms disappear in 5 to 14 days; however, there appears to be a phase of secondary or chronic abstinence which may last for 2 to 6 months characterized by insomnia, irritability, muscular aches, and autonomic instability.

In the treatment of physical dependence on hydromorphone hydrochloride tablets, the patient may be detoxified by gradual reduction of the dosage, although this is unlikely to be necessary in the terminal cancer patient. If abstinence symptoms become severe, the patient may be detoxified with methadone. Temporary administration of tranquilizers and sedatives may aid in reducing patient anxiety. Gastrointestinal disturbances or dehydration should be treated accordingly.

OVERDOSAGE

Serious overdosage with hydromorphone hydrochloride tablets is characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. In serious overdosage, particularly following intravenous injection, apnea, circulatory collapse, cardiac arrest and death may occur.

In the treatment of overdosage, primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. A potentially serious oral ingestion, if recent, should be managed with gut decontamination. In unconscious patients with a secure airway, instill activated charcoal (30 to 100 g in adults, 1 to 2 g/kg in infants) via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal.

Opioid-tolerant patient: Since tolerance to the respiratory and CNS depressant effects of opioids develops concomitantly with tolerance to their analgesic effects, serious respiratory depression due to an acute overdose is unlikely to be seen in opioid-tolerant patients receiving the usual therapeutic dosage of hydromorphone hydrochloride tablets for chronic pain. *Note:* In such an individual who is physically dependent on opioids, administration of the usual dose of an opioid antagonist will precipitate an acute withdrawal syndrome. The severity will depend on the degree of physical dependence and the dose of the antagonist administered. If necessary to treat serious respiratory depression in the physically-dependent patient, the opioid antagonist should be administered with care and by titration, using fractional (one fifth to one tenth) doses of the antagonist.

Non-tolerant patient: The opioid antagonist, naloxone, is a specific antidote against respiratory depression which may result from overdosage, or unusual sensitivity to hydromorphone hydrochloride tablets. A dose of naloxone (usually given as a test dose of 0.4 mg, followed by up to 2 mg if needed) should be administered intravenously, if possible, simultaneously with respiratory resuscitation. The dose can be repeated in 3 minutes. Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression. Naloxone should be administered cautiously to persons who are known, or suspected to be physically dependent on hydromorphone hydrochloride tablets (*see Opioid-tolerant patient*).

Since the duration of action of hydromorphone hydrochloride tablets may exceed that of the antagonist, the patient should be kept under continued surveillance; repeated doses of the antagonist may be required to maintain adequate respiration. Apply other supportive measures when indicated.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSAGE AND ADMINISTRATION

The usual starting dose for hydromorphone hydrochloride tablets USP is 2 mg to 4 mg, orally, every 4 to 6 hours. Appropriate use of hydromorphone hydrochloride tablets USP, 8 mg must be decided by careful evaluation of each clinical situation.

A gradual increase in dose may be required if analgesia is inadequate, as tolerance develops, or if pain severity increases. The first sign of tolerance is usually a reduced duration of effect.

SAFETY AND HANDLING INSTRUCTIONS

Hydromorphone hydrochloride tablets pose little risk of direct exposure to health care personnel and should be handled and disposed of prudently in accordance with hospital or institutional policy. Significant absorption from dermal exposure is unlikely. Patients and their families should be instructed to flush any hydromorphone hydrochloride tablets that are no longer needed.

Access to abusable drugs such as hydromorphone hydrochloride tablets presents an occupational hazard for addiction in the health care industry. Routine procedures for handling controlled substances developed to protect the public may not be adequate to protect health care workers. Implementation of more effective accounting procedures and measures to restrict access to drugs of this class (appropriate to the practice setting) may minimize the risk of self-administration by health care providers.

HOW SUPPLIED

Hydromorphone hydrochloride tablets USP, 8 mg are available as a white to off-white arc triangle shaped tablet debossed with a bisected "M" on one side and a split "8" on the other side.

Bottles of 100 ..... NDC No. 0406-3249-01

STORAGE: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). (See USP Controlled Room Temperature). Protect from light.

A Schedule CII Narcotic. DEA Order Form is required.

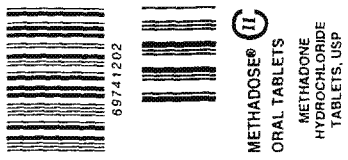
Mallinckrodt Inc.
St. Louis, MO 63134 U.S.A.

MG #19750

tyco Healthcare

Mallinckrodt

Rev 050104



METHADOSE® ORAL TABLETS

METHADONE HYDROCHLORIDE TABLETS, USP

II

Rx only

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS:
Code of Federal Regulations, Title 21, Sec. 291.505

METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

A METHADONE PRODUCT, WHEN USED AS AN ANALGESIC, MAY BE DISPENSED IN ANY LICENSED PHARMACY.

DESCRIPTION

Methadone Hydrochloride, USP 6-(dimethylamino)-4, 4-diphenyl-3-heptanone hydrochloride, is a white, crystalline material that is water soluble. Its molecular weight is 345.91.

Each METHADOSE® Oral Tablet contains: 5 mg (0.0145 mmol) or 10 mg (0.029 mmol) Methadone Hydrochloride, USP.

Each tablet also contains Dibasic Calcium Phosphate USP, Microcrystalline Cellulose NF, Magnesium Stearate NF, Colloidal Silicon Dioxide NF, Pregelatinized Starch NF, and Stearic Acid NF.

CLINICAL PHARMACOLOGY

Methadone hydrochloride is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or temporary maintenance in narcotic addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

A parenteral dose of 8 to 10 mg of methadone is approximately equivalent in analgesic effect to 10 mg of morphine. With single-dose administration, the onset and duration of analgesic action of the two drugs are similar.

When administered orally, methadone is approximately one half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE *(see boxed Note)*

1. For relief of severe pain.
2. For detoxification treatment of narcotic addiction.
3. For temporary maintenance treatment of narcotic addiction.

NOTE

If methadone is administered for treatment of heroin dependence for more than 3 weeks, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy. Maintenance treatment is permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during the critical period of his/her stay or whose enrollment has been verified in a program which has approval for maintenance treatment with methadone.

CONTRAINDICATION

Hypersensitivity to methadone.

WARNINGS

METHADOSE® Oral Tablets are for oral administration only and *must not* be used for injection. It is recommended that METHADOSE® Oral Tablets, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Methadone hydrochloride, a narcotic, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE — **METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP ON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.**

Interaction With Other Central Nervous System Depressants — Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Anxiety — Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure — The respiratory depressant effects of the methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions — Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect — The administration of methadone may result in severe hypotension in an individual whose ability to maintain his/her blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Use in Ambulatory Patients — Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy — Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Methadone is not recommended for obstetric analgesia because its long duration of action increases the probability of respiratory depression in the newborn.

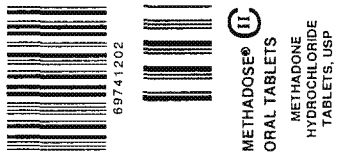
Use in Children — Methadone is not recommended for use as an analgesic in children, since documented clinical experience has been insufficient to establish a suitable dosage regimen for the pediatric age group.

PRECAUTIONS

Drug Interactions:

Pentazocine — **Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given pentazocine.**

Rifampin — The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.



Monoamine Oxidase (MAO) Inhibitors — Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Special-Risk Patients — Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

Acute Abdominal Conditions — The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

ADVERSE REACTIONS

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION, RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated if the ambulatory patient lies down.

Other adverse reactions include the following:

Central Nervous System — Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal — Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular — Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genitourinary — Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic — Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Hematologic — Reversible thrombocytopenia has been described in a narcotics addict with chronic hepatitis.

OVERDOSAGE

Symptoms — Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment — Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a nontolerant person, especially a child, takes a large dose of methadone, effective narcotic antagonists are available to counteract the potentially lethal respiratory depression. ***The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas the antagonists act for much shorter periods (1 to 3 hours).*** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered naloxone is the drug of choice to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON NARCOTICS, THE ADMINISTRATION OF THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME. THE SEVERITY OF THIS SYNDROME WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE DOSE OF THE ANTAGONIST ADMINISTERED. THE USE OF A NARCOTIC ANTAGONIST IN SUCH A PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT MUST BE USED TO TREAT SERIOUS RESPIRATORY DEPRESSION IN THE PHYSICALLY DEPENDENT PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST.

DOSAGE AND ADMINISTRATION

For Relief of Pain — Dosage should be adjusted according to the severity of the pain and the response of the patient. Occasionally, it may be necessary to exceed the usual dosage recommended in cases of exceptionally severe pain or in those patients who have become tolerant to the analgesic effect of narcotics.

The usual adult dosage is 2.5 mg to 10 mg every three or four hours as necessary.

For Detoxification Treatment — THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than four weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg/day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for 2 to 3 days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 3 weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

If the patient is unable to ingest oral medication, parenteral administration may be substituted.

HOW SUPPLIED

METHADOSE® Oral Tablets (Methadone Hydrochloride Tablets, USP):

5 mg white, scored tablets (Identified METHADOSE 5) NDC 0406-6974-34: Bottles of 100 tablets

10 mg white, scored tablets (Identified METHADOSE 10) NDC 0406-3454-34: Bottles of 100 tablets

Keep tightly closed. Dispense in a tight, light-resistant container. Store at controlled room temperature, 15° to 30° C (59° to 86° F) [see USP].

METHADOSE® is a registered trademark of Mallinckrodt Inc.

Mallinckrodt Inc
St. Louis, MO 63134, USA

tyco Healthcare

Mallinckrodt

MG #13774

Rev 122902

98018

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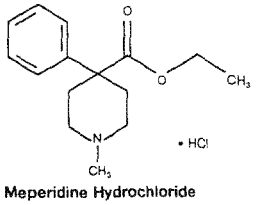
MEPERIDINE
HYDROCHLORIDE
TABLETS, USP
(50 mg and 100 mg)
Rx only

MEPERIDINE HYDROCHLORIDE TABLETS, USP (50 mg and 100 mg) C II
Rx only

DESCRIPTION

Meperidine hydrochloride, a narcotic analgesic, is ethyl 1-methyl-4-phenylisonipecotate hydrochloride, a white crystalline substance with a melting point of 186° C to 189° C. It is readily soluble in water and has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling. It has the following structural formula:



Meperidine Hydrochloride

$C_{15}H_{21}NO_2 \cdot HCl$ M.W.=283.80

Each MEPERIDINE HYDROCHLORIDE, USP 50 mg tablet for oral administration contains:
Meperidine Hydrochloride, USP.....50 mg

Each MEPERIDINE HYDROCHLORIDE, USP 100 mg tablet for oral administration contains:
Meperidine Hydrochloride, USP.....100 mg

In addition, each MEPERIDINE HYDROCHLORIDE, USP tablet contains the following inactive ingredients: Dibasic Calcium Phosphate, Magnesium Stearate, Microcrystalline Cellulose, Povidone, Pregelatinized Starch, Stearic Acid, and Talc.

CLINICAL PHARMACOLOGY

Meperidine hydrochloride is a narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation.

There is some evidence which suggests that meperidine may produce less smooth muscle spasm, constipation, and depression of the cough reflex than equianalgesic doses of morphine. Meperidine, in 60 mg to 80 mg parenteral doses, is approximately equivalent in analgesic effect to 10 mg of morphine. The onset of action is slightly more rapid than with morphine, and the duration of action is slightly shorter. Meperidine is significantly less effective by the oral than by the parenteral route, but the exact ratio of oral to parenteral effectiveness is unknown.

INDICATIONS AND USAGE

For the relief of moderate to severe pain.

CONTRAINDICATIONS

Hypersensitivity to meperidine.

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear, but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic overdose. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with meperidine. If a narcotic is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of morphine are administered over the course of several hours while the patient's condition and vital signs are under careful observation. (Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown.)

Solutions of meperidine hydrochloride and barbiturates are chemically incompatible.

WARNINGS

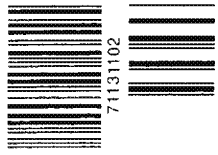
Drug Dependence. Meperidine can produce drug dependence of the morphine type and therefore has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of meperidine, and it should be prescribed and administered with the same degree of caution appropriate to the use of morphine. Like other narcotics, meperidine is subject to the provisions of the Federal narcotic laws.

Interaction with Other Central Nervous System Depressants. MEPERIDINE SHOULD BE USED WITH GREAT CAUTION AND IN REDUCED DOSAGE IN PATIENTS WHO ARE CONCURRENTLY RECEIVING OTHER NARCOTIC ANALGESICS, GENERAL ANESTHETICS, PHENOTHIAZINES, OTHER TRANQUILIZERS (SEE DOSAGE AND ADMINISTRATION), SEDATIVE-HYPNOTICS (INCLUDING BARBITURATES), TRICYCLIC ANTIDEPRESSANTS AND OTHER CNS DEPRESSANTS (INCLUDING ALCOHOL). RESPIRATORY DEPRESSION, HYPOTENSION, AND PROFOUND SEDATION OR COMA MAY RESULT.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of meperidine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, meperidine must be used with extreme caution and only if its use is deemed essential.

Asthma and Other Respiratory Conditions. Meperidine should be used with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, and patients with preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect. The administration of meperidine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the administration of drugs such as phenothiazines or certain anesthetics.



Usage in Ambulatory Patients. Meperidine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.
Meperidine, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Usage in Pregnancy and Lactation. Meperidine should not be used in pregnant women prior to the labor period, unless in the judgement of the physician the potential benefits outweigh the possible hazards, because safe use in pregnancy prior to labor has not been established relative to possible adverse effects on fetal development.

Meperidine appears in the milk of nursing mothers receiving the drug.

PRECAUTIONS

Supraventricular Tachycardias. Meperidine should be used with caution in patients with atrial flutter and other supraventricular tachycardias because of a possible vagolytic action which may produce a significant increase in the ventricular response rate.

Convulsions. Meperidine may aggravate preexisting convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

Acute Abdominal Conditions. The administration of meperidine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients. Meperidine should be given with caution and the initial dose should be reduced in certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS

The major hazards of meperidine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Other adverse reactions include:

Nervous System. Euphoria, dysphoria, weakness, headache, agitation, tremor, uncoordinated muscle movement, severe convulsions, transient hallucinations and disorientation, visual disturbances.

Gastrointestinal. Dry mouth, constipation, biliary tract spasm.

Cardiovascular. Flushing of the face, tachycardia, bradycardia, palpitation, hypotension (see WARNINGS), syncope.

Genitourinary. Urinary retention.

Allergic. Pruritus, urticaria, other skin rashes.

Other. Antidiuretic effect.

OVERDOSAGE

Symptoms. Serious overdosage with meperidine is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment. Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone hydrochloride, is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including meperidine. Therefore, an appropriate dose of this antagonist should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

In cases of overdosage with Meperidine Hydrochloride Tablets, USP, the stomach should be evacuated by emesis or gastric lavage.

NOTE: In an individual physically dependent on narcotics, the administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of the antagonist administered. The use of narcotic antagonist in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only one-fifth to one-tenth the usual initial dose administered.

DOSAGE AND ADMINISTRATION

For Relief of Pain

Dosage should be adjusted according to the severity of the pain and the response of the patient. Meperidine is less effective orally than with parenteral administration. The dose of Meperidine Hydrochloride Tablets, USP should be proportionally reduced (usually by 25 to 50 percent) when administered concomitantly with phenothiazines and many other tranquilizers since they potentiate the action of meperidine.

Adults. The usual dosage is 50 mg to 150 mg orally, every 3 or 4 hours as necessary.

Children. The usual dosage is 0.5 mg/lb to 0.8 mg/lb orally, up to the adult dose, every 3 or 4 hours as necessary.

HOW SUPPLIED

Each Meperidine Hydrochloride Tablet, USP (50 mg) is available as a round, white to off-white scored tablet debossed with a semi-circle arc "7113" on one side and a Ⓜ on the other side.
Bottles of 100.....NDC 0406-7113-01

Each Meperidine Hydrochloride Tablet, USP (100 mg) is available as a round, white to off-white tablet debossed with a semi-circle arc "7115" on one side and a Ⓜ on the other side.
Bottles of 100.....NDC 0406-7115-01

Store at controlled room temperature 15° to 30° C (59° to 86° F).

Dispense in a tight, light-resistant container as defined in the USP.

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tyco Healthcare

Mallinckrodt

Mallinckrodt Inc.
St. Louis, MO 63134
MG #15760

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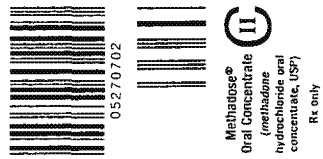


Methadose® Oral Concentrate

(methadone hydrochloride oral concentrate, USP) C II

Rx only

FOR ORAL USE ONLY

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS

Code of Federal Regulations, Title 42, Sec. 8

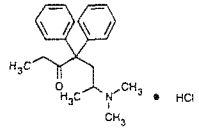
METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF OPIOID ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY OPIOID TREATMENT PROGRAMS (AND AGENCIES, PRACTITIONERS, OR INSTITUTIONS BY FORMAL AGREEMENT WITH THE PROGRAM SPONSOR) CERTIFIED BY THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION AND APPROVED BY THE DESIGNATED STATE AUTHORITY.

CERTIFIED TREATMENT PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL OPIOID TREATMENT STANDARDS (42 CFR 8.12).

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE STANDARDS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM CERTIFICATION AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

DESCRIPTION

METHADOSE® Oral Concentrate (methadone hydrochloride oral concentrate, USP) is supplied as a cherry flavored liquid concentrate. The liquid concentrate contains 10 mg of methadone hydrochloride per mL. Methadone hydrochloride, 3-heptanone, 6-(dimethylamino)-4, 4-diphenyl-, hydrochloride is a white, crystalline, odorless powder. It is soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerin. It is present in Methadose® as the racemic mixture. Methadone hydrochloride has a melting point of 235° C, a pKa of 8.25 to 10.12, a solution (1 in 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water and a molecular weight of 345.91. Its molecular formula is $C_{21}H_{27}NO \cdot HCl$ and its structural formula is:



Other Ingredients: Artificial Cherry Flavor, Citric Acid Anhydrous USP, FD&C Red No. 40, D&C Red No. 33, Methylparaben NF, Poloxamer 407 NF, Propylene Glycol USP, Propylparaben NF, Purified Water USP, Sodium Citrate Dihydrate USP, Sucrose NF.

CLINICAL PHARMACOLOGY

Methadone hydrochloride is a synthetic opioid analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation, detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE

1. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
2. Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

Maintenance and detoxification treatment is permitted to be undertaken only by certified treatment programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during the critical period of his stay, and whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS

Hypersensitivity to methadone.

WARNINGS

METHADOSE® is for oral administration only. This preparation must not be injected. It is recommended that METHADOSE®, if dispensed, be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Asthma and Other Respiratory Conditions: Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease, or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of opioids may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hypotensive Effect: The administration of methadone may result in severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

PRECAUTIONS

General: Special-Risk Patients: Methadone should be given with caution and the initial dose reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients: Use in Ambulatory Patients: Methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of *potentially hazardous tasks such as driving a car or operating machinery. The patient* should be cautioned accordingly.

Methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.

Alcohol and other CNS depressants may produce an additive CNS depression, when *taken with this product, and should be avoided.*

Drug Interactions: Interaction with Pentazocine: Patients who are addicted to opioids or who are on the methadone maintenance program may experience withdrawal symptoms when given pentazocine.

Interaction with Other Central Nervous System Depressants: Methadone should be *used with caution and in reduced dosage in patients who are concurrently receiving* other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Interaction with Rifampin: The concurrent administration of rifampin may possibly reduce the blood concentrations of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Interaction with Monoamine Oxidase (MAO) Inhibitors: Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or in those who have received such agents within fourteen days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Anxiety: Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of opioid abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of opioid symptoms and is ineffective for relief of general anxiety.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether methadone has a potential for *carcinogenesis, mutagenesis, or impairment of fertility.*

Pregnancy: *Teratogenetic Effects:* Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenetic Effects: Babies born to mothers who have been taking opioids *regularly prior to delivery will be physically dependent. The withdrawal signs include* irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

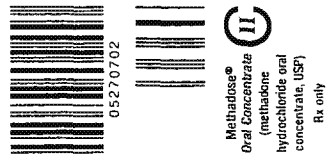
Nursing Mothers: It is not known whether methadone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Opioid Withdrawal: During the induction phase of methadone maintenance treatment, patients are being withdrawn from opioids and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side-effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from opioids: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, gooseflesh, fever, chilliness, alternating with flushing, restlessness, irritability, "sleepy yen," weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration: Initially, the dosage of methadone should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce the following effects.



Methadose® Oral Concentrate

(methadone hydrochloride oral concentrate, USP)

Rx only

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER OPIOID ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.

The most frequently observed adverse reactions include light-headedness, dizziness, *sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in* ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated in the ambulatory patient if he lies down.

Other adverse reactions include the following: Central Nervous System - Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastro-Intestinal - Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular - Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genito-Urinary - Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic - Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Maintenance on a Stabilized Dose: During prolonged administration of methadone, as in an opioid treatment program, there is a gradual, yet progressive, disappearance of side-effects over a period of several weeks. However, constipation and sweating often persist.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Methadone hydrochloride, an opioid, is a Schedule *II controlled substance under the Federal Controlled Substances Act. Appropriate* security measures should be taken to safeguard stocks of methadone against diversion.

ABUSE AND DEPENDENCE: METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP UPON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

OVERDOSAGE

Symptoms: Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, especially a child, takes a large dose of methadone, effective opioid antagonists are available to counter-act the potentially lethal respiratory depression. **THE PHYSICIAN MUST REMEMBER, HOWEVER, THAT METHADONE IS A LONG-ACTING DEPRESSANT (THIRTY-SIX TO FORTY-EIGHT HOURS), WHEREAS THE ANTAGONISTS ACT FOR MUCH SHORTER PERIODS (ONE TO THREE HOURS).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the opioid antagonist as needed. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered opioid antagonists, naloxone hydrochloride, nalorphine hydrochloride, or levallorphan tartrate are the drugs of choice to reverse signs of intoxication. These agents should be given repeatedly until the patient's status remains satisfactory. The hazard that the opioid antagonist will further depress respiration is less likely with the use of naloxone.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON OPIOIDS, THE ADMINISTRATION OF THE USUAL DOSE OF AN OPIOID ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME. THE SEVERITY OF THIS SYNDROME WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE DOSE OF THE ANTAGONIST ADMINISTERED. THE USE OF AN OPIOID ANTAGONIST IN SUCH PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT MUST BE USED TO TREAT SERIOUS RESPIRATORY DEPRESSION IN THE PHYSICALLY DEPENDENT PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST.

DOSAGE AND ADMINISTRATION

For Detoxification Treatment: Patients with two or more unsuccessful detoxification episodes within a 12-month period must be assessed by the treatment program physician for other forms of treatment. A program shall not admit a patient for more than two detoxification treatment episodes in one year.

Short-Term Detoxification: A short-term detoxification treatment program may not exceed 30 days. No medications may be dispensed to patients in short-term detoxification treatment for unsupervised or take-home use.

Long-Term Detoxification: A long-term detoxification program is for a period of more than 30 days but may not exceed 180 days. The conditions under which medication for unsupervised use by patients in long-term detoxification treatment are to be determined by the program medical director.

In detoxification, the patient may receive methadone when determined to be appropriate by the program physician. The dosage schedules indicated below are recommended but could be varied in the judgement of the program physician. Initially, a single oral dose of 15 to 20 mg of methadose will often be sufficient to suppress withdrawal symptoms. The initial dose shall not exceed 30 mg. Additional methadose may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. The total dose for the first day shall not exceed 40 mg, unless the program physician documents that 40 mg did not suppress opiate abstinence symptoms. Forty mg per day, in single or divided doses, will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for two to three days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at two-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20 percent of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may *be needed. If methadose is administered for more than 180 days, the procedure is* considered to have progressed from detoxification to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

For Maintenance Treatment: Interim Maintenance Treatment: A patient may be admitted into an interim maintenance treatment program while awaiting admission to a program providing comprehensive maintenance treatment. Interim maintenance may not be provided for more than 120 days in a 12-month period. Admission must be voluntary, and the patient must have become addicted at least one year before admission for treatment except as provided in the opioid treatment standards. No medications may be dispensed to patients in Interim Maintenance Treatment for unsupervised or take-home use.

In maintenance treatment, the initial dosage of methadone should control the abstinence symptoms that follow withdrawal of opioid drugs but should not be so great as to cause sedation, respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the opioid tolerance of the new patient. If such a patient has been a heavy user of opioids up to the day of admission, he may be given 20 mg four to eight hours later, or up to 30 mg in an initial, single dose. If the patient enters with little or no opioid tolerance (e.g., if he has recently been released from jail or other confinement), the initial dosage may be one-half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional methadose may be administered as needed. Any first-day dose in excess of 40 mg must be documented by the program physician. Any deviation from the approved labeling (dose, frequency, or conditions of use) must also be documented. Subsequently, the dosage should be adjusted individually, as tolerated and required. In comprehensive maintenance programs, any patient may receive a single take-home dose for a day that the clinic is closed for business, including State and Federal holidays. This is in addition to other take-home allowances given as follows. All other doses shall be taken under supervision. For the first 90 days of *treatment, the take-home supply shall be limited to a single dose per week. After* demonstrating satisfactory adherence to the program requirements for this first 90 days, the patient may receive two take-home doses per week. With continuing adherence to the program requirements for 180 days, the patient may receive a three-day take-home supply. For the remainder of the first year of treatment, the patient may be given a maximum 6-day supply of take-home medication. After 1 year of continuous treatment, the patient may be given a maximum 2-week supply of take-home medication. After 2 years of continuous treatment, the patient may be given a maximum one-month supply of take-home medication, but must make monthly visits. A regular review of dosage level should be made by the program physician, with careful consideration given to reduction of dosage as indicated on an individual basis.

Special Considerations for a Pregnant Patient: Caution shall be taken in the maintenance treatment of pregnant patients. Dosage levels shall be kept as low as possible if continued methadone treatment is deemed necessary. It is the responsibility of the program sponsor to assure that each female patient be fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone.

Special Limitations: Treatment of Patients under Age Eighteen: The safety and effectiveness of methadone for use in the treatment of adolescents have not been proven by adequate clinical study.

A Patient under 18 years of age is required to have had two documented unsuccessful attempts at short-term detoxification treatment or drug-free treatment within a 12-month period to be eligible for maintenance treatment.

No person under 18 years of age may be admitted to maintenance treatment unless a *parent, legal guardian, or responsible adult designated by the State authority consents* in writing to such treatment.

HOW SUPPLIED

METHADOSE® Oral Concentrate (methadone hydrochloride oral concentrate, USP) *10 mg per mL is supplied as a red, cherry flavored liquid concentrate in one liter bottles* (NDC 0406-0527-10).

Preserve in tight containers, protected from light. Store at Controlled Room Temperature 20° - 25° C (68° - 77° F); brief excursions permitted between 15° - 30° C (59° - 86° F).

Methadose® is a registered trademark of Mallinckrodt Inc.

Mallinckrodt Inc.
St. Louis, MO 63134, USA

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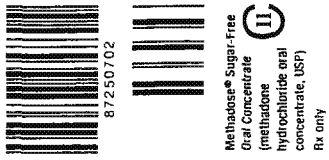
MG # 15332 Rev. 072302



Methadose® Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate, USP) dye-free, sugar-free, unflavored

Rx only

FOR ORAL USE ONLY

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER OPIOID ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.

The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated in the ambulatory *patient if he lies down.*

Other adverse reactions include the following: Central Nervous System - Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastro-Intestinal - Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular - Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genito-Urinary - Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic - Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Maintenance on a Stabilized Dose: During prolonged administration of methadone, as in an opioid treatment program, there is a gradual, yet progressive, disappearance of side-effects over a period of several weeks. However, constipation and sweating often persist.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Methadone hydrochloride, an opioid, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

ABUSE AND DEPENDENCE: METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP UPON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

OVERDOSAGE

Symptoms: Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a non-tolerant person, especially a child, takes a large dose of methadone, effective opioid antagonists are available to counter-act the potentially lethal respiratory depression. **THE PHYSICIAN MUST REMEMBER, HOWEVER, THAT METHADONE IS A LONG-ACTING DEPRESSANT (THIRTY-SIX TO FORTY-EIGHT HOURS), WHEREAS THE ANTAGONISTS ACT FOR MUCH SHORTER PERIODS (ONE TO THREE HOURS).** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the opioid antagonist as needed. If the diagnosis is correct and respiratory depression is *due only to overdosage of methadone, the use of respiratory stimulants is not* indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered opioid antagonists, naloxone hydrochloride, nalorphine hydrochloride, or levallorphan tartrate are the drugs of choice to reverse signs of intoxication. These agents should be given repeatedly until the patient's status remains satisfactory. The hazard that the opioid antagonist will further depress respiration is less likely with the use of naloxone.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON OPIOIDS, THE ADMINISTRATION OF THE USUAL DOSE OF AN OPIOID ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME. THE SEVERITY OF THIS SYNDROME WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE DOSE OF THE ANTAGONIST ADMINISTERED. THE USE OF AN OPIOID ANTAGONIST IN SUCH PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT MUST BE USED TO TREAT SERIOUS RESPIRATORY DEPRESSION IN THE PHYSICALLY DEPENDENT PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST.

DOSAGE AND ADMINISTRATION

For Detoxification Treatment: Patients with two or more unsuccessful detoxification episodes within a 12-month period must be assessed by the treatment program physician for other forms of treatment. A program shall not admit a patient for more than two detoxification treatment episodes in one year.

Short-Term Detoxification: A short-term detoxification treatment program may not exceed 30 days. No medications may be dispensed to patients in short-term detoxification treatment for unsupervised or take-home use.

Long-Term Detoxification: A long-term detoxification program is for a period of more than 30 days but may not exceed 180 days. The conditions under which medication for unsupervised use by patients in long-term detoxification treatment are to be determined by the program medical director.

In detoxification, the patient may receive methadone when determined to be appropriate by the program physician. The dosage schedules indicated below are recommended but could be varied in the judgement of the program physician. Initially, a single oral dose of 15 to 20 mg of methadose will often be sufficient to suppress withdrawal symptoms. The initial dose shall not exceed 30 mg. Additional methadose may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. The total dose for the first day shall not exceed 40 mg, unless the program physician documents that 40 mg did not suppress opiate abstinence symptoms. Forty mg per day, in single or divided doses, will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for two to three days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at two-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20 percent of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadose is administered for more than 180 days, the procedure is considered to have progressed from detoxification to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

For Maintenance Treatment: Interim Maintenance Treatment: A patient may be admitted into an interim maintenance treatment program while awaiting admission to a program providing comprehensive maintenance treatment. Interim maintenance may not be provided for more than 120 days in a 12-month period. Admission must be *voluntary, and the patient must have become addicted at least one year before* admission for treatment except as provided in the opioid treatment standards. No medications may be dispensed to patients in Interim Maintenance Treatment for unsupervised or take-home use.

In maintenance treatment, the initial dosage of methadone should control the abstinence symptoms that follow withdrawal of opioid drugs but should not be so great as to cause sedation, respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the opioid tolerance of the new patient. If such a patient has been a heavy user of opioids up to the day of admission, he may be given 20 mg four to eight hours later, or up to 30 mg in an initial, single dose. If the patient enters with little or no opioid tolerance (e.g., if he has recently been released from jail or other confinement), the initial dosage may be one-half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional methadose may be administered as needed. Any first-day dose in excess of 40 mg must be documented by the program physician. Any deviation from the approved labeling (dose, frequency, or conditions of use) must also be documented. Subsequently, the dosage should be adjusted individually, as tolerated and required. In comprehensive maintenance programs, any patient may receive a single take-home dose for a day that the clinic is closed for business, including State and Federal holidays. This is in addition to other take-home allowances given as follows. All other doses shall be taken under supervision. For the first 90 days of treatment, the take-home supply shall be limited to a single dose per week. After demonstrating satisfactory adherence to the program requirements for this first 90 days, the patient may receive two take-home doses per week. With continuing adherence to the program requirements for 180 days, the patient may receive a three-day take-home supply. For the remainder of the first year of treatment, the patient may be given a maximum 6-day supply of take-home medication. After 1 year of continuous treatment, the patient may be given a maximum 2-week supply of take-home medication. After 2 years of continuous treatment, the patient may be given a maximum one-month supply of take-home medication, but must make monthly visits. A regular review of dosage level should be made by the program physician, with careful consideration given to reduction of dosage as indicated on an individual basis.

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No person under 18 years of age may be admitted to maintenance treatment unless a *parent, legal guardian, or responsible adult designated by the State authority consents* in writing to such treatment.

HOW SUPPLIED

Methadose® Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate, USP) 10 mg per mL is supplied in one liter bottles (NDC 0406-8725-10).

Preserve in tight containers, protected from light. Store at Controlled Room Temperature 20° - 25° C (68° - 77° F); brief excursions permitted between 15° - 30° C (59° - 86° F).

Methadose® is a registered trademark of Mallinckrodt Inc.

Mallinckrodt Inc.
St. Louis, MO 63134, USA

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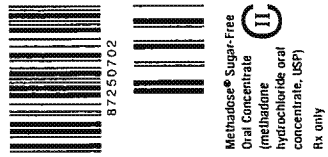
MG # 16428

Rev. 072502



Methadose® Sugar-Free Oral Concentrate (methadone hydrochloride oral concentrate, USP) dye-free, sugar-free, unflavored

C II

Rx only

FOR ORAL USE ONLY

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS

Code of Federal Regulations, Title 42, Sec. 8

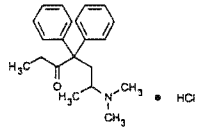
METHADONE PRODUCTS WHEN USED FOR THE TREATMENT OF OPIOID ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY OPIOID TREATMENT PROGRAMS (AND AGENCIES, PRACTITIONERS, OR INSTITUTIONS BY FORMAL AGREEMENT WITH THE PROGRAM SPONSOR) CERTIFIED BY THE SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMINISTRATION AND APPROVED BY THE DESIGNATED STATE AUTHORITY.

CERTIFIED TREATMENT PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL OPIOID TREATMENT STANDARDS (42 CFR 8.12).

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE STANDARDS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM CERTIFICATION AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

DESCRIPTION

Methadose® Sugar-Free Oral Concentrate is a liquid concentrate of methadone hydrochloride. The liquid concentrate contains 10 mg of methadone hydrochloride per mL. Methadone hydrochloride, 3-heptanone, 6-(dimethylamino)-4, 4-diphenyl-, hydrochloride is a white, crystalline, odorless powder. It is soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in ether and in glycerin. It is present in Methadose® as the racemic mixture. Methadone hydrochloride has a melting point of 235° C, a pKa of 8.25 to 10.12, a solution (1 in 100) pH between 4.5 and 6.5, a partition coefficient of 117 at pH 7.4 in octanol/water and a molecular weight of 345.91. Its molecular formula is $C_{21}H_{27}NO \cdot HCl$ and its structural formula is:



Other Ingredients: Citric Acid Anhydrous USP, Purified Water USP, Sodium Benzoate NF.

CLINICAL PHARMACOLOGY

Methadone hydrochloride is a synthetic opioid analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation, detoxification or maintenance in opioid addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE

1. Detoxification treatment of opioid addiction (heroin or other morphine-like drugs).
2. Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

Maintenance and detoxification treatment is permitted to be undertaken only by certified treatment programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during the critical period of his stay, and whose enrollment has been verified in a program which has been certified for maintenance treatment with methadone.

CONTRAINDICATIONS

Hypersensitivity to methadone.

WARNINGS

Methadose® Sugar-Free Oral Concentrate is for oral administration only. This preparation must not be injected. It is recommended that Methadose® Sugar-Free Oral Concentrate, if dispensed, be packaged in child-resistant containers and kept out of reach of children to prevent accidental ingestion.

Asthma and Other Respiratory Conditions: Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease, or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of opioids may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution, and only if it is deemed essential.

Acute Abdominal Conditions: The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hypotensive Effect: The administration of methadone may result in severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

PRECAUTIONS

General: Special-Risk Patients: Methadone should be given with caution and the initial dose reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture. The usual precautions should be observed and the possibility of respiratory depression should be kept in mind.

Information for Patients: Use in Ambulatory Patients: Methadone, like all opioids, may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other opioids, may produce orthostatic hypotension in ambulatory patients.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this product, and should be avoided.

Drug Interactions: Interaction with Pentazocine: Patients who are addicted to opioids or who are on the methadone maintenance program may experience withdrawal symptoms when given pentazocine.

Interaction with Other Central Nervous System Depressants: Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Interaction with Rifampin: The concurrent administration of rifampin may possibly reduce the blood concentrations of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Interaction with Monoamine Oxidase (MAO) Inhibitors: Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or in those who have received such agents within fourteen days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Anxiety: Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of opioid abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of opioid symptoms and is ineffective for relief of general anxiety.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether methadone has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Pregnancy: *Teratogenetic Effects:* Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Methadone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenetic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting, and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Labor and Delivery: As with all opioids, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

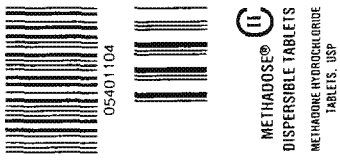
Nursing Mothers: It is not known whether methadone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from methadone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Opioid Withdrawal: *During the induction phase of methadone maintenance treatment,* patients are being withdrawn from opioids and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side-effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from opioids: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, gooseflesh, fever, chilliness, alternating with flushing, restlessness, irritability, "sleepy yen," weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration: Initially, the dosage of methadone should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce the following effects.



METHADOSE® DISPERSIBLE TABLETS

METHADONE HYDROCHLORIDE TABLETS, USP

Rx only

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS:
Code of Federal Regulations, Title 21, Sec. 291.505

METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

DESCRIPTION

Methadone Hydrochloride, USP 6-(dimethylamino)-4, 4-diphenyl-3-heptanone hydrochloride, is a white, crystalline material that is water soluble. However, the METHADOSE® Dispersible Tablet preparation of Methadone Hydrochloride, USP has been specially formulated with insoluble excipients to deter the use of this drug by injection. Its molecular weight is 345.91.

Each METHADOSE® Dispersible Tablet contains: 40 mg (0.116 mmol) Methadone Hydrochloride, USP.

Each tablet also contains Dibasic Calcium Phosphate USP, Microcrystalline Cellulose NF, Magnesium Stearate NF, Colloidal Silicon Dioxide NF, Pregelatinized Starch NF, and Stearic Acid NF.

CLINICAL PHARMACOLOGY

Methadone hydrochloride is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or maintenance in narcotic addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

When administered orally, methadone is approximately one half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE

1. Detoxification treatment of narcotic addiction (heroin or other morphine-like drugs).
2. Maintenance treatment of narcotic addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

If methadone is administered for treatment of heroin dependence for more than 3 weeks, the procedure passes from treatment of the acute withdrawal *syndrome (detoxification) to maintenance therapy. Maintenance treatment is* permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for *medical conditions other than addiction and who requires temporary* maintenance during the critical period of his/her stay or whose enrollment has been verified in a program which has approval for maintenance treatment with *methadone.*

CONTRAINDICATION

Hypersensitivity to methadone.

WARNINGS

METHADOSE® Dispersible Tablets are for oral administration only. This preparation contains insoluble excipients and therefore *must not* be injected. It is recommended that METHADOSE® Dispersible Tablets, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Methadone hydrochloride, a narcotic, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE — **METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP ON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.**

Interaction With Other Central Nervous System Depressants — Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Anxiety — Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the *dosage of methadone. The action of methadone in maintenance treatment is* limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure — The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions — Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect — The administration of methadone may result in severe hypotension in an individual whose ability to maintain his/her blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Use in Ambulatory Patients — *Methadone may impair the mental and/or physical* abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy — Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS

Drug Interactions:

Pentazocine — **Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given pentazocine.**

Rifampin — The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Monoamine Oxidase (MAO) Inhibitors — Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Special-Risk Patients — Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

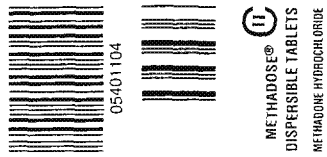
Acute Abdominal Conditions — *The administration of methadone or other* narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

ADVERSE REACTIONS

Heroin Withdrawal — During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, "sleepy yen", weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal *cramps, body aches, involuntary twitching and kicking movements, anorexia,* nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration — initially, the dosage of methadone should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce the following effects:

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION, RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.



The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated if the ambulatory patient lies down.

Other adverse reactions include the following:

Central Nervous System — Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal — Dry mouth, anorexia, constipation, and biliary tract spasm.

Cardiovascular — Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genitourinary — Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic — Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Hematologic — Reversible thrombocytopenia has been described in a narcotics addict with chronic hepatitis.

Maintenance on a Stabilized Dose — During prolonged administration of methadone, as in a methadone maintenance treatment program, there is a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

OVERDOSAGE

Symptoms — Serious overdosage of methadone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and, sometimes, bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment — Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. If a nontolerant person, especially a child, takes a large dose of methadone, effective narcotic antagonists are available to counteract the potentially lethal respiratory depression. ***The physician must remember, however, that methadone is a long-acting depressant (36 to 48 hours), whereas the antagonists act for much shorter periods (1 to 3 hours).*** The patient must, therefore, be monitored continuously for recurrence of respiratory depression and treated repeatedly with the narcotic antagonist as needed. If the diagnosis is correct and respiratory depression is due only to overdosage of methadone, the use of respiratory stimulants is not indicated.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Intravenously administered naloxone is the drug of choice to reverse signs of intoxication. Because of the relatively short half-life of naloxone as compared with methadone, repeated injections may be required until the status of the patient remains satisfactory. Naloxone may also be administered by continuous intravenous infusion.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

NOTE: IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON NARCOTICS, THE ADMINISTRATION OF THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME. THE SEVERITY OF THIS SYNDROME WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE DOSE OF THE ANTAGONIST ADMINISTERED. THE USE OF A NARCOTIC ANTAGONIST IN SUCH A PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT MUST BE USED TO TREAT SERIOUS RESPIRATORY DEPRESSION IN THE PHYSICALLY DEPENDENT PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST.

DOSAGE AND ADMINISTRATION

For Detoxification Treatment — THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than four weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg/day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for 2 to 3 days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 3 weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

For Maintenance Treatment — In maintenance treatment, the initial dosage of methadone should control the abstinence symptoms that follow withdrawal of narcotic drugs but should not be so great as to cause sedation, respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the narcotic tolerance of the new patient. If such a patient has been a heavy user of heroin up to the day of admission, he/she may be given 20 mg 4 to 8 hours later or 40 mg in a single oral dose. If the patient enters treatment with little or no narcotic tolerance (eg, if he/she has recently been released from jail or other confinement), the initial dosage may be one half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional 10-mg doses may be administered as needed. Subsequently, the dosage should be adjusted individually, as tolerated and required, up to a level of 120 mg daily. The patient will initially ingest the drug under observation daily, or at least 6 days a week, for the first 3 months. After demonstrating satisfactory adherence to the program regulations for at least 3 months, the patient may be permitted to reduce to 3 times weekly the occasions when he/she must ingest the drug under observation. The patient shall receive no more than a 2-day take-home supply. With continuing adherence to the program's requirements for at least 2 years, he/she may then be permitted twice-weekly visits to the program for drug ingestion under observation, with a 3-day take-home supply. A daily dose of 120 mg or more shall be justified in the medical record. Prior approval from state authority and the Food and Drug Administration is required for any dose above 120 mg administered at the clinic and for any dose above 100 mg to be taken at home. A regular review of dosage level should be made by the responsible physician, with careful consideration given to reduction of dosage as indicated on an individual basis. A new dosage level is only a test level until stability is achieved.

Special Considerations for a Pregnant Patient — Caution shall be taken in the maintenance treatment of pregnant patients. Dosage levels shall be kept as low as possible if continued methadone treatment is deemed necessary. It is the responsibility of the program sponsor to assure that each female patient be fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone.

Special Limitations — Treatment of Patients Under Age 18

1. The safety and effectiveness of methadone for use in the treatment of adolescents have not been proved by adequate clinical study. Special procedures are therefore necessary to assure that patients under age 16 will not be admitted to a program and that patients between 16 and 18 years of age will be admitted to maintenance treatment only under limited conditions.
2. Patients between 16 and 18 years of age who were enrolled and under treatment in approved programs on December 15, 1972 may continue in maintenance treatment. No new patients between 16 and 18 years of age may be admitted to a maintenance treatment program after March 15, 1973, unless a parent, legal guardian, or responsible adult designated by the state authority completes and signs Form FD 2635, "Consent for Methadone Treatment".

   Methadone treatment of new patients between the ages of 16 and 18 years will be permitted after December 15, 1972, only with a documented history of 2 or more unsuccessful attempts at detoxification and a documented history of dependence on heroin or other morphine-like drugs beginning 2 years or more prior to application for treatment. No patient under age 16 may be continued or started on methadone treatment after December 15, 1972, but these patients may be detoxified and retained in the program in a drug-free state for follow-up and aftercare.
3. Patients under age 18 who are not placed on maintenance treatment may be detoxified. Detoxification may not exceed 3 weeks. A repeat episode of detoxification may not be initiated until 4 weeks after the completion of the previous detoxification.

HOW SUPPLIED

METHADOSE® Dispersible Tablets (Methadone Hydrochloride Tablets, USP):

40 mg (white, quadrisect) (Identified METHADOSE 40) NDC 0406-0540-34: Bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

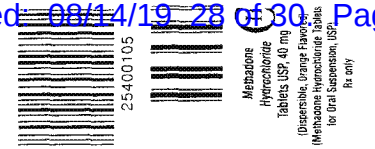
METHADOSE® is Mallinckrodt Inc.'s brand of Methadone Hydrochloride, USP.

tyco Healthcare

Mallinckrodt

Mallinckrodt Inc.
St. Louis, MO 63134, USA

Rev 112104 MG #13776
98017



Methadone Hydrochloride Tablets USP, 40 mg
(Dispersible, Orange Flavored)
(Methadone Hydrochloride Tablets for Oral Suspension, USP)

CII

For Methadone Treatment Programs

Rx only

CONDITIONS FOR DISTRIBUTION AND USE OF METHADONE PRODUCTS:
Code of Federal Regulations,
Title 21, Sec. 291.505

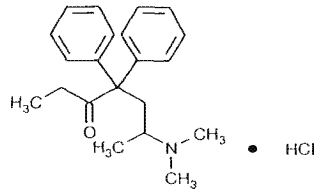
METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

DESCRIPTION

Methadone hydrochloride tablets for oral suspension, (3-heptanone, 6-(dimethylamino)-4,4-diphenyl-hydrochloride), is a white, essentially odorless, bitter-tasting, crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. Methadone hydrochloride has a pKa of 8.25 in water at 20°C. Its molecular weight is 345.91 and it has the following structural formula.



$C_{21}H_{27}NO \cdot HCl$ MW = 345.91

The preparation of methadone hydrochloride for oral suspension has been specially formulated with insoluble excipients to deter the use of this drug by injection.

Each methadone hydrochloride tablet for oral suspension contains:

Methadone Hydrochloride USP..... 40 mg (0.116 mmol)

In addition, each tablet also contains: colloidal silicon dioxide NF; dibasic calcium phosphate dihydrate, USP; magnesium stearate, NF; microcrystalline cellulose, NF; pregelatinized starch, NF; stearic acid, NF; orange blend: FD&C yellow #6, FD&C yellow #6 lake, and FD&C yellow #5 lake; orange flavor.

CLINICAL PHARMACOLOGY

Methadone hydrochloride is a synthetic narcotic analgesic with *multiple actions quantitatively similar to those of morphine, the most* prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or maintenance in narcotic addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS AND USAGE

1. Detoxification treatment of narcotic addiction (heroin or other morphine-like drugs).
2. Maintenance treatment of narcotic addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

If methadone is administered for treatment of heroin dependence for more than three weeks, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy. Maintenance treatment is permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during this critical period of his/her stay or whose enrollment has been verified in a program which has approval for maintenance treatment with methadone.

CONTRAINDICATIONS

Hypersensitivity to methadone.

WARNINGS

Methadone hydrochloride tablets are for oral administration only. This preparation contains insoluble excipients and therefore *must not* be injected. It is required that the methadone hydrochloride tablets, if dispensed, be packaged in *child-resistant containers and kept out of the reach of children* to prevent accidental ingestion.

Methadone hydrochloride, a narcotic, is a Schedule II controlled *substance under the Federal Controlled Substances Act.* Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE - METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP ON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

Interaction with Other Central Nervous System Depressants - Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). *Respiratory depression, hypotension, and* profound sedation or coma may result.

Anxiety - Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure - The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions - Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect - The administration of methadone may result in severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Use in Ambulatory Patients - Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy - Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS

Drug Interactions:

Pentazocine - Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given an opioid agonist-antagonist, such as pentazocine.

Rifampin - The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Monoamine Oxidase (MAO) Inhibitors - Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine - Blood levels of desipramine have increased with concurrent methadone therapy.

Special-Risk Patients - Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

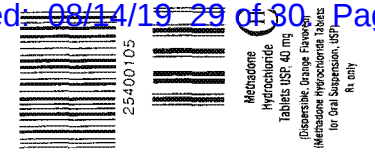
Acute Abdominal Conditions - The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

ADVERSE REACTIONS

Heroin Withdrawal - During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, "sleepy yen", weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration - Initially, the dosage of methadone should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce the following effects.

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.



The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe chronic pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated in the ambulatory patient if he lies down.

Other adverse reactions include the following:

Central Nervous System - Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal - Dry mouth, anorexia, constipation and biliary tract spasm.

Cardiovascular - Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genitourinary - Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic - Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Hematologic - Reversible thrombocytopenia has been described in a narcotics addict with chronic hepatitis.

Maintenance on a Stabilized Dose - During prolonged administration of methadone, as in a methadone maintenance treatment program, there is a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

OVERDOSAGE

Signs and Symptoms - Methadone is an opioid and produces effects similar to those of morphine. Symptoms of overdose begin within seconds after intravenous administration and within minutes of nasal, oral, or rectal administration. Prominent symptoms are miosis, respiratory depression, somnolence, coma, cool clammy skin, skeletal muscle flaccidity that may progress to hypotension, apnea, bradycardia, and death. Noncardiac pulmonary edema may occur, and monitoring of heart filling pressures may be helpful.

Treatment - To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference® (PDR®)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and usual drug kinetics in your patient.

Initial management of opioid overdose should include establishment of a secure airway and support of ventilation and perfusion. Naloxone may be given to antagonize opioid effects, but the airway must be secured as vomiting may ensue. **The duration of methadone effect is much longer (36 to 48 hours) than the duration of naloxone effect (1 to 3 hours), and repeated doses (or continuous intravenous infusion) of naloxone may be required.**

If the patient has chronically abused opioids, administration of naloxone may precipitate a withdrawal syndrome that may include yawning, tearing, restlessness, sweating, dilated pupils, piloerection, vomiting, diarrhea, and abdominal cramps. If these symptoms develop, they should abate quickly as the effects of naloxone dissipate.

If methadone has been taken by mouth, protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of methadone.

NOTE

IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON NARCOTICS, THE ADMINISTRATION OF THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME. THE SEVERITY OF THIS SYNDROME WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE DOSE OF THE ANTAGONIST ADMINISTERED. THE USE OF A NARCOTIC ANTAGONIST IN SUCH A PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT MUST BE USED TO TREAT SERIOUS RESPIRATORY DEPRESSION IN THE PHYSICALLY DEPENDENT PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST.

DOSAGE AND ADMINISTRATION

Methadone Hydrochloride Tablets for Oral Suspension are intended for dispersion in a liquid prior to oral administration of the prescribed dose.

For Detoxification Treatment - THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than 4 weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg/day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for 2 to 3 days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 3 weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

For Maintenance Treatment - In maintenance treatment, the initial dosage of methadone should control the abstinence symptoms that follow withdrawal of narcotic drugs but should not be so great as to cause sedation, respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the narcotic tolerance of the new patient. If such a patient has been a heavy user of heroin up to the day of admission, he/she may be given 20 mg 4 to 8 hours later or 40 mg in a single oral dose. If the patient enters treatment with little or no narcotic tolerance (e.g., if he/she has recently been released from jail or other confinement), the initial dosage may be one half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional 10-mg doses may be administered as needed. Subsequently, the dosage should be adjusted individually, as tolerated and required, up to a level of 120 mg daily. The patient will initially ingest the drug under observation daily, or at least 6 days a week, for the first 3 months. After demonstrating satisfactory adherence to the program regulations for at least 3 months, the patient may be permitted to reduce to 3 times weekly the occasions when he/she must ingest the drug under observation. The patient shall receive no more than a 2-day take-home supply. With continuing adherence to the program's requirements for at least 2 years, he/she may then be permitted twice-weekly visits to the program for drug ingestion under observation, with a 3-day take-home supply. A daily dose of 120 mg or more shall be justified in the medical record. Prior approval from state authority and the Food and Drug Administration is required for any dose above 120 mg administered at the clinic and for any dose above 100 mg to be taken at home. A regular review of dosage level should be made by the responsible physician, with careful consideration given to reduction of dosage as indicated on an individual basis. A new dosage level is only a test level until stability is achieved.

Special Considerations for a Pregnant Patient - Caution shall be taken in the maintenance treatment of pregnant patients. Dosage levels shall be kept as low as possible if continued methadone treatment is deemed necessary. It is the responsibility of the program sponsor to assure that each female patient be fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone.

Special Limitations-
Treatment of Patients Under Age 18

1. The safety and effectiveness of methadone for use in the treatment of adolescents have not been proved by adequate clinical study. Special procedures are therefore necessary to assure that patients under age 16 will not be admitted to a program and that patients between 16 and 18 years of age will be admitted to maintenance treatment only under limited conditions.
2. Patients between 16 and 18 years of age who were enrolled and under treatment in approved programs on December 15, 1972, may continue in maintenance treatment. No new patients between 16 and 18 years of age may be admitted to a maintenance treatment program after March 15, 1973, unless a parent, legal guardian, or responsible adult designated by the state authority completes and signs Form FD 2635, "Consent for Methadone Treatment."

   Methadone treatment of new patients between the ages of 16 and 18 years will be permitted after December 15, 1972, only with a documented history of 2 or more unsuccessful attempts at detoxification and a documented history of dependence on heroin or other morphine-like drugs beginning 2 years or more prior to application for treatment. No patient under age 16 may be continued or started on methadone treatment after December 15, 1972, but these patients may be detoxified and retained in the program in a drug-free state for follow-up and aftercare.
3. Patients under age 18 who are not placed on maintenance treatment may be detoxified. Detoxification may not exceed 3 weeks. A repeat episode of detoxification may not be initiated until 4 weeks after the completion of the previous detoxification.

HOW SUPPLIED

Each methadone hydrochloride tablet for oral suspension contains 40 mg of methadone hydrochloride USP. It is available as a speckled orange colored, rounded rectangular tablet, debossed with "M" over "2540" on one side, a quadrisect on the other with an orange odor.

Bottles of 100.....NDC No. 0406-2540-01

Dispense in a tight, light-resistant container as defined in the USP.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Mallinckrodt Inc.
St. Louis, MO 63134, U.S.A.

tyco Healthcare

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Rev 012705 MG #20680

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